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61

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Neuropsychological deficits associated with small unilateral thalamic lesions. C. W. Wallesch, H. H. Kornhuber, T. Kunz and R. J. Brunner 141

Oscillopsia and retinal slip: evidence supporting a clinical test. Eugene R. Wist, Th. Brandt and S. Krafczyk 153

Chronic demyelinating neuropathy associated with benign IgM paraproteinaemia. I. S. Smith, S. N. Kahn, B. W. Lacey, R. H. M. King, R. A. Eames, D. J. Whybrew and P. K. Thomas 169

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Notices of recent publications 223

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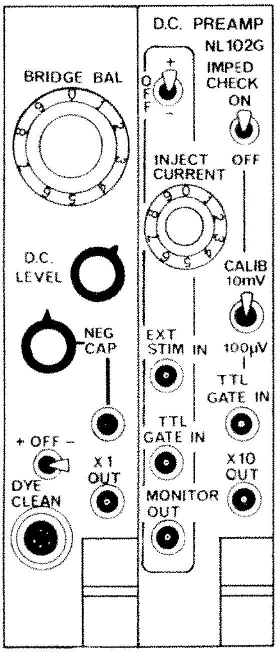
Notices of recent publications 223



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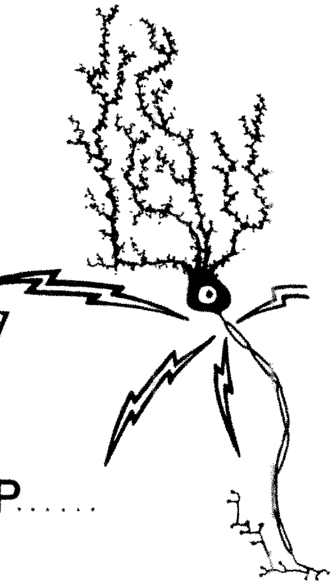

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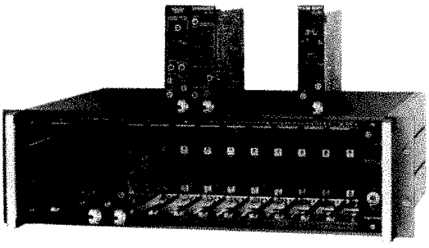

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THE ROLE OF CUTANEOUS AFFERENTS IN POSITION SENSE, KINAESTHESIA, AND MOTOR FUNCTION OF THE HAND

by ERIK MOBERG

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SUMMARY

In reconstructive surgery and rehabilitation work, for decades it has been a basic problem for the author to discover which of the peripheral receptor systems provide the primary information on position, motion and degree of load (proprioception). At one time, joint receptors were accepted as the dominant source and more recently musculocutaneous receptors, whereas little attention has been given to cutaneous factors.

A number of clinical observations, however, have indicated the importance of cutaneous afferents and this prompted the present study. There are no means of isolating the joint receptors in order to test them alone, but the fact that very good kinaesthesia can be present in their absence militates against their importance. The cutaneous and musculotendinous factors were therefore studied independently in the forearm and hand in test subjects, partly by means of an extensive nerve blocking technique, but also in experiments of the type devised by Gelfan and Carter (1967). The latter proved to be much less simple than had earlier been claimed.

The results of the experiments indicated that no kinaesthetic information reaching conscious level could be shown to arise from the musculocutaneous system, whereas the cutaneous afferents appeared to provide the dominant input. As this system can be readily examined and can be moved surgically to parts in need of proprioception, the practical consequences are obvious.

It was also observed that signals arising from skin that is displaced over contracting muscle bellies or moving tendons remote from the activated parts of the limb could constitute an important source of error, overlooked in earlier studies.

INTRODUCTION

The old problem, not yet solved, of what has been variously termed kinaesthetic sensibility, position sense, muscle sense or proprioception has been discussed in several excellent and exhaustive reviews (Goodwin, 1976; McCloskey, 1978; Willis and Coggeshall, 1978). From these reviews it seems clear that receptors in skin, joints or muscles can neither be given an exclusive role nor be excluded from participation. It is fair to say that in today's discussion the joint receptors, once dominant, are losing ground; that muscle receptors, formerly often excluded or neglected, are gaining ground; and that cutaneous receptors, so often forgotten, are now sometimes given a role.

The following investigations were performed not by a professional physiologist but by a surgeon who desired a more reliable physiological basis for his own reconstructive work (Moberg, 1976, 1978). Observations on many patients during four decades of reconstructive limb surgery, together with the results of some simple experiments, also on man, and mainly by blocking the afferent input from different parts of the forearm and hand, have suggested that the role of cutaneous receptors in position sense and kinaesthesia has been greatly underestimated. It has also seemed likely that in previous experiments aimed at disclosing the role of muscle receptors in proprioception, effects from cutaneous receptors might have been an unrecognized source of error.

OBSERVATIONS

Some Clinical Observations

During operations, patients with an ulnar and/or median block at wrist level, together with a block of the dorsal branches, can be totally unaware of the active movements their fingers often perform. When the surgeon asks them to keep their fingers still and tells them that their movements are interfering with his work, their apologies often include the statement that they did not know, or did not feel, that they were moving their fingers. In such cases the cutaneous sensibility of the hand is almost eliminated, together with at least the major input from the joint afferents. Since muscle afferents from the long flexors and extensors are intact, it appears that these cannot alone subserve an adequate sense of movement of the fingers.

A similar conclusion can be drawn from the following cases.

Case 1. A man aged 34 years, had received a knife cut about 4 cm proximal to the left elbow on the previous day. He had a total loss of ulnar nerve sensibility from about 5 cm below the elbow, but full motor action of the long flexors and extensors. The intrinsic muscles of the little finger were paralysed (fig. 1). At operation I found the ulnar nerve totally severed about 4 cm above elbow level. The patient was quite unable to appreciate passive changes in position of the little finger, nor could he bring it, without the help of vision, into a demanded position. Only in full active extension or flexion was he able to give the position of the finger, that is, when strong *effort* in either direction was applied. Of course in this case the profundus muscle to the little finger must have had an anomalous innervation, probably not just an unusually high separation of the ulnar nerve into different branches.

A similar phenomenon occurred in the experiments to be described below, on the perception of active and passive movements by normal subjects (p. 10). If the subject, under cutaneous anaesthesia, had lost the ability to bring the thumb to a demanded position when making a strong effort of extension or flexion, he was still able to say when he had fully extended his thumb or had fully flexed it. It is not known whether he actually felt that the thumb was in these positions or whether this was only his conclusion from the muscular *effort* that he had made to bring the thumb to these extreme positions. In these cases the long muscles were intact but local cutaneous and joint receptors eliminated.

Case 2. A 21-year old man had a deep glass cut at the right elbow. According to the report from the operating surgeon, the median and ulnar nerves were totally severed at elbow level and they were sutured. However, a very detailed examination on the next day revealed marked anomalies in the nerve supply to the hand. Median and ulnar sensibility in the hand was totally lost in the usual volar areas of the nerves. The proximal half of the dorsal aspect of the proximal phalanx of the ring finger had normal sensibility, probably from the radial nerve. Full extension with normal power was retained in all digits. But the fingers had, anomalously, retained, not normal, but a fair power of flexion, all from the long muscles. Which long muscles were working was not possible to distinguish exactly but probably some of the profundi. All the intrinsic muscles were paralysed. The ring finger could be flexed through half the normal range, but with less than half the normal power.

This patient could easily report the position into which the metacarpophalangeal joint of the ring finger had been brought, and could also reproduce the position with the ring finger of the other hand. But it was totally impossible for him to report the position of the two interphalangeal joints of the ring finger, over which cutaneous sensibility was absent. Even when he was told to use the active muscles against good resistance he was totally unaware of the position of these joints.

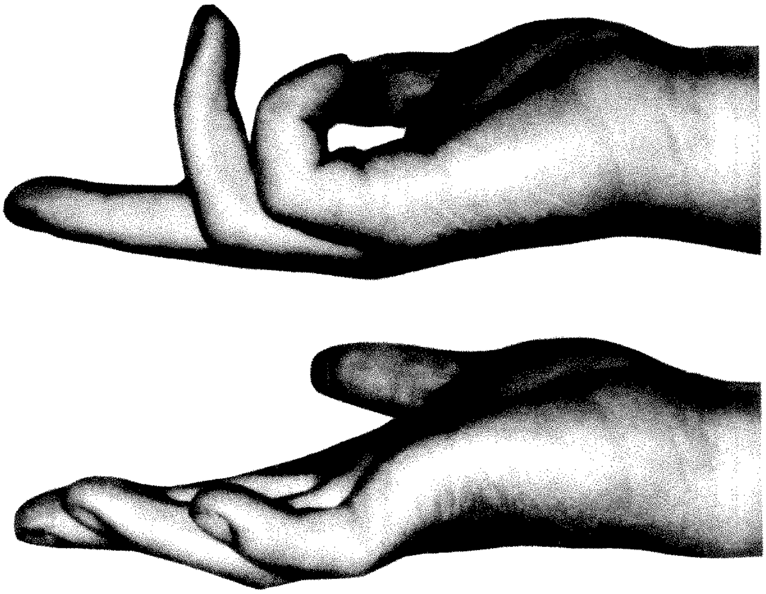

FIG. 1. *Case 1.* Complete severance of ulnar nerve 4 cm proximal to elbow. Anomalous normal function in both long flexors of the little finger (*see text*); normal function of long extensor; loss of sensation in ulnar distribution from 5 cm distal to elbow; loss of position sense in little finger except for awareness of full flexion or full extension after maximal voluntary effort.

Case 3. A patient had sustained a crush of the proximal interphalangeal joint of a middle finger. He stated correctly, without seeing the hand, that the finger in the joint region was not flexing when he tried to flex it, but was just telescoping. It seems likely that cutaneous afferents gave him this information.

Observations from Reconstructive Surgery

It is an everyday observation that a leg, in which the hip joint has been totally removed and substituted by artificial material, has adequate position sense in spite of loss of all joint receptors (B. Stener, personal communication). A detailed study by Grigg *et al.* (1973) has shown no, or no significant, differences from the normal.

Our own tests, performed with the technique described for the index finger (*see below*, p. 11) on the perception of passive movements of digits after total removal of the joint structures and replacement by silastic implants, have shown no differences from the normal. Cross and McCloskey (1973) also reported normal perception of passive movements of digits with silastic implants. In these cases, as in that of the hip, the preservation of position sense and kinaesthesia must have been due to receptors in skin, in muscle, or in both.

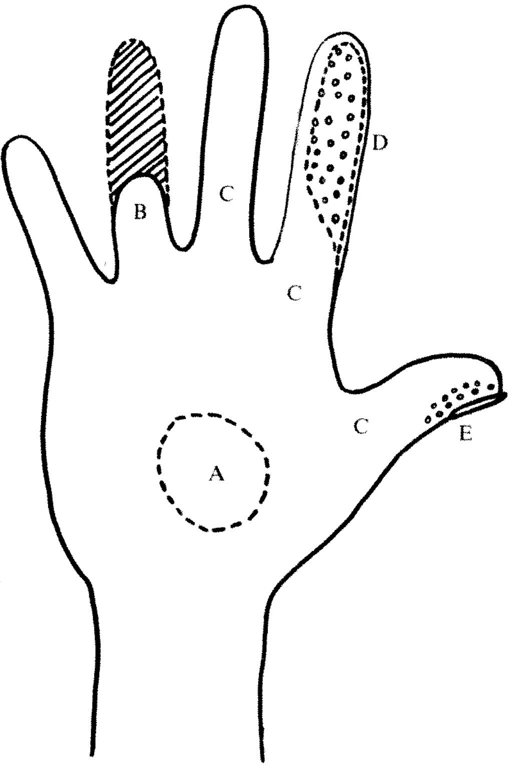

FIG. 2. *Case 4.* Right hand. Tendons transferred from ring finger to index finger and thumb; transfer of neurovascular skin flap from ring finger to index (*see text*). A, site of total median nerve lesion with scar; tendons of flexor pollicis longus and both long flexors of index also severed. B, *amputated* ring finger, from which tendons and ulnar skin with nervous and vascular supply were transferred. C, cutaneous areas without sensory function. D, normal ulnar nerve sensibility from the skin transferred to the index finger. E, thumb sensibility from normal radial overlap.

Case 4. I wish to describe in more detail a patient with surgery on the hand. He was a heavy labourer. He had a deep lesion in the palm of the right hand, which healed with extensive scarring after infection. All branches of the median nerve were severed at the injury and also the tendons of the long flexor of the thumb and both long flexors to the index finger. The motor nerve to the thenar muscles was intact. All sensibility to the volar aspects of the thumb, the index, the middle finger and the radial half of the ring finger was lost as is usual with this lesion. Due to the extensive scarring the nerve branches and the tendons were considered beyond repair. I therefore sacrificed parts of the ring finger (figs. 2 and 3) and by transferring the tendon, made the superficialis tendon a thumb flexor and the ring profundus an index flexor. But the significant factor in the present context was that I also moved the volar skin of the ring finger, innervated by the ulnar nerve and accompanied by the intact nerve and vessels, to the volar surface of the index finger.

Fig. 3 shows the hand seventeen years after this operation. The texture and the colour of the skin showed that the thumb (where the dorsal nerves had a somewhat larger supply on the sides than usual), the index and the little finger were being extensively used; the middle finger, however, in spite of its two normal flexors,

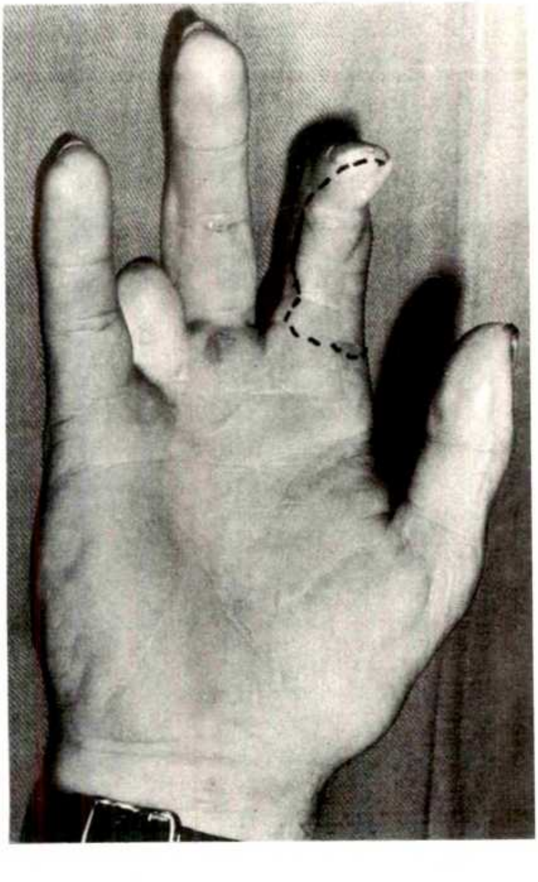

FIG. 3. *Case 4.* Right hand, seventeen years after surgery. Broken line = neurovascular island flap, with normal sensibility. Volar aspect of middle finger is anaesthetic.

hardly at all. It lacked all volar sensibility. The patient also stated that the hand had a real gripping function but that the middle finger did not contribute to it. He said 'it does not follow'.

So in this case, seventeen years after surgery, there was an unusual situation. In the index finger there was normal volar sensibility from the ulnar nerve of the ring finger (fig. 2), while there was no skin sensibility in the remaining part of the skin originally innervated by the median nerve branches. The dorsal surfaces of the index and middle fingers, however, were still innervated by nerve branches entering the hand across the dorsum of the wrist, and thus retained some cutaneous sensibility. The same branches also supply some innervation to the metacarpophalangeal and proximal interphalangeal joints. Before testing the patient's awareness of passive movements imposed on the index and middle fingers by the technique described below (p. 11), the dorsal nerves were therefore blocked by subcutaneous infiltration anaesthesia at wrist level.

The result was that in the index, with its volar skin innervated by the ulnar nerve, the sense of passive movement was found to be normal. It seems impossible that the joint receptors in the index finger could have been reinnervated by sprouting from the ulnar nerve into the chronically degenerated digital and articular branches of the median, particularly in an adult, and much more likely that the cutaneous receptors were responsible for the normal proprioception in this finger after the operation.

In the middle finger the sense of passive movement and position was found to be absent. The innervation of its three extrinsic muscles and of its interossei was intact, so their muscle spindles were unable to provide proprioception in the absence of any cutaneous input.

A similar case was tested in the same way twelve years after reconstructive surgery with the same results.

Accordingly, a variety of clinical observations suggest that muscle receptors alone cannot give a sense of position and movement. In this connection it must be remembered that many forearm muscles are working across as many as five joints and that many combinations of different joint positions can correspond with exactly the same length and tension in the long finger flexors and extensors.

In reconstructive surgery, especially of the hand, tendon transfer is a routine procedure. The ability of patients to learn to use the transferred muscles, even in movements in which their new functions may be antagonistic to their original functions, furnishes remarkable evidence of the adaptability of cerebral motor output, and is of great neurological interest. The origins of muscles are usually not moved. In some cases it is only necessary to attach the tendon to a new insertion, but in others, part of the muscle must also be moved. Thus when flexor carpi ulnaris or radialis is to be used as an extensor of the wrist or fingers, the distal part of the muscle has to be brought round on to the dorsum of the forearm. Extensor indicis proprius is very useful as a replacement for extensor pollicis longus and can also be used as an adductor of the thumb. Flexor superficialis of the ring finger can be used for many different purposes. Some of these transfers hardly need any re-education for their new functions, others require a substantial amount. For example, in surgical rehabilitation of the upper limb in tetraplegia (Moberg, 1976, 1978, 1981), it has recently become the practice to fashion the posterior half of the deltoid into an elbow extensor by joining it with free tendon grafts to the tendon of the paralysed triceps. The muscle 'knows' its new function as soon as the arm is out of plaster. By contrast, brachioradialis, which is normally a flexor of the elbow, will not act properly as a wrist extensor or a finger flexor unless it is first provided with an antagonist at the elbow. If triceps is paralysed, therefore, the reconstruction must begin with a deltoid transfer. Re-education of brachioradialis can then proceed, but requires time. But when brachioradialis is to be used as a pronator, no prior transfer of triceps is necessary and no re-education is required.

A Source of Error and How it was Discovered

It has been suggested in the Introduction that effects from cutaneous receptors may have been an unrecognized source of error in experiments aimed at disclosing the role of muscle receptors in position sense and kinaesthesis. Tshlenow (1927) and later Halpern (1949) claimed that a loss of ability to detect when skin was painlessly lifted and moved over a part of the body went parallel with the loss of the sense of position and movement in the same region. About twenty years ago my collaborator S. H. Nahigian and I tried to evaluate the role of cutaneous sensibility in kinaesthesia in active movements of the hand. We used an arrangement for testing the active movements which was similar to the one described below (p. 10). In tests on the thumb, index and little finger we tried to evaluate the loss of ability to perceive positions after injections of local anaesthetic. At the time the dominating teaching was that a 'joint sense' was responsible for kinaesthesia. In our experiments all nerves to the joints must have been included in the anaesthetic areas. The observations of Tshlenow and Halpern were at that time almost forgotten and a possible role of cutaneous afferents in kinaesthesia was either not discussed at all or was denied. When the anaesthesia extended proximally as far as the wrist level on the volar as well as the dorsal aspect, the subject lost the ability to discriminate position in the little finger and the index finger. The digits could be moved actively over their full range but the subjects were unable to reach demanded positions or to perceive the extent of passive movements. The thumb, however, often reacted differently. The sense of position was lost but the subjects retained some small part of their awareness of the direction of passive movements, and more so of active movements. Also, there were clear, important individual variations, very similar to those found in later experiments, for example, by Gandevia and McCloskey (1976). All attempts to explain the difference between the fingers by the existence of individual variations in innervation or by the fact that the little finger was exclusively innervated by the ulnar nerve, the index by the median and radial nerve, the thumb perhaps also from the musculocutaneous nerve and having an adductor supplied by the ulnar nerve, were in vain. The experiments were never published.

But as shown above, contrary to general opinion, clinical observations indicated that cutaneous receptors might be important. So the working hypothesis was formed that information was obtained not only by the compression and stretching of the skin over the finger joints during movements, but also from skin regions overlying the contracting muscles and moving tendons remote from the joints. If cutaneous receptors in the forearm play this second role, then the special situation of the thumb compared to the other digits tested would be intelligible. The four long tendons of the thumb, the special arrangements around the snuffbox and the great mobility of the basal carpometacarpal joint of the thumb might displace the unanaesthetized skin of the forearm much more than the movements of the other digits. Also, subjects with strong muscle bellies might get more information from the remote cutaneous receptors than those with slender arms. More such information might be expected during active than during passive movements. Individual variations could also depend on different elasticity of the skin and so age could be involved.

Active Thumb and Passive Index Finger Movements

The experiments are an extension of those described in the preceding section, and include two different tests on three subjects. The subjects were male surgeons, who were aware of the hypothesis to be tested.

The first series of tests required the subjects to move their thumbs actively into demanded positions of flexion or extension. These movements impose considerable displacements on the skin of the forearm which overlies the long muscles and tendons of the thumb (*see* preceding section). After the performances had been mastered, the effect on proprioception of blockade of all afferents distal to the wrist was tested. Finally the whole cutaneous sleeve of the forearm was infiltrated with local anaesthetic to the level of the epicondyles, and the tests were repeated. Tests with passive thumb movements were omitted as they had already been carried out in the previous experiments with S. H. Nahigian.

In the second series the subjects were tested for the accuracy of their perception of the angles into which the proximal interphalangeal joint of the index finger had been passively placed. These movements cause less disturbance to the skin of the forearm than that caused by active movements of the thumb. The effects of blockade by local anaesthetics were tested as for the thumb. Active movements of index finger were also tested, but the results did not differ from those for passive movements, and are therefore not reported.

The anaesthetic used was 2 per cent lignocaine with adrenaline (except once when 2 per cent mepivacaine without adrenaline was used). The median and ulnar nerves were blocked at wrist level by direct nerve injection and the dorsal radial branches by subcutaneous injections. The whole forearm cutaneous sleeve was anaesthetized by a considerable number of cutaneous injections, up to the level of the epicondyles.

It is not possible to limit the injection to the sites where the nerves penetrate the fascia, as the anatomy here is quite individual. Therefore, for the more proximal levels it was necessary to use up to 30 ml of the anaesthetic, which was enough to produce general effects, not during the test but some time after the end of the tests when the absorption from the arm was at its peak.

All the results are from experiments in which the anaesthesia of the forearm was complete; different results were obtained in one case with incomplete anaesthesia of a small ulnar area.

During the experiments I frequently checked that the power and range of movement of the long flexors and extensors were not influenced by the injections.

Active thumb movement. The left hand and forearm of the subject were placed comfortably on a soft support with a diaphragm between the thumb and the rest of the hand (fig. 4). The thumb could be moved up and down. An almost weightless indicator was fixed to the nail and indicated on a scale the position of the thumb. The wrist was in about 15 deg extension, the forearm semipronated, and the elbow about 90 deg flexed. All the subjects performed most of the movements at the metacarpophalangeal joint, less at the interphalangeal and almost none at the carpometacarpal joint. The subjects were given extensive training, in which they were told the angles into which they had to place the thumb, and were allowed to see the scale. They were trained for about half an hour on the first day, and for about half an hour before every test, both with and without vision. The tests were begun and completed with vision excluded. A careful control was also kept so that information could not be obtained from clues such as sound or friction.

Between each trial the subjects were instructed to move the thumb up and down a few times to allow a 'fresh start' for the next positioning. The subjects were simply asked to go to a particular angle ('90', '10', etc., fig. 4), in steps of 10 deg with all angles randomly represented in equal numbers. From the initial position the thumb was always moved in both directions several times to exclude memory of the starting point. Tests were performed with 5 to 10 s intervals. The forearm was exposed to avoid information from the shirt sleeve.

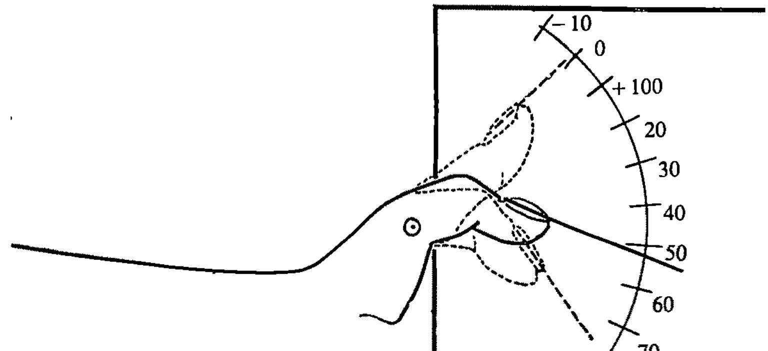

FIG. 4 Arrangement for measuring active flexions and extensions of thumb (*see text*).

TABLE 1 ACTIVE THUMB POSITIONING WITH AND WITHOUT DIFFERENT LEVELS OF CUTANEOUS ANAESTHESIA LONG MUSCLES UNIMPAIRED IN ALL EXPERIMENTS

			Error			
		No. of	*Maximum*			
Subject		*obs.*	*Neg.*	*Pos.*	*Mean*	*SD*
1	No anaesthesia	76	20	20	−2	8
2		67	10	10	0	6
3		68	10	10	1	5
1	Anaesthesia from wrist	27	90	0	37	26
2	level distally; volar	40	30	40	6	17
3	and dorsal aspects	40	30	40	1	16
1	Added anaesthesia of	26	60	60	−28	31
2	whole forearm	40	30	50	19	19
3	cutaneous sleeve	40	40	40	−11	19

The results from the thumb experiments are given in Table 1. The performance of all three subjects has clearly deteriorated from stage 2 to 3, after the addition of local anaesthesia of the forearm. Contrary to the findings in the experiments with passive movement of the index finger described below, in the thumb experiments one could observe how the skin was displaced by the tendons and muscles not only over the snuffbox but also well proximally in the forearm. All three subjects had strong muscles. The tests also included the end positions −10 and +90 deg. It was observed that when the subject had lost the ability to bring the thumb to a demanded intermediate position he nevertheless retained the ability to move it into full flexion or extension. The subjects were unable to say whether they felt that the thumb actually was in one of these positions or only concluded from the muscular effort that the thumb must have reached this position. Full flexions (+90 deg) and full extensions (−10 deg) are included in Table 1, but the small number of tests with these positions does not significantly influence the results.

Passive movements of the index finger. The left index finger of the subject was placed on a small table (fig. 5). Elevated 5 mm from the surface of the table to ensure that no information could be obtained from contact, it was fixed with a padded strip around the base. The forearm was semipronated and the ulnar border of the hand

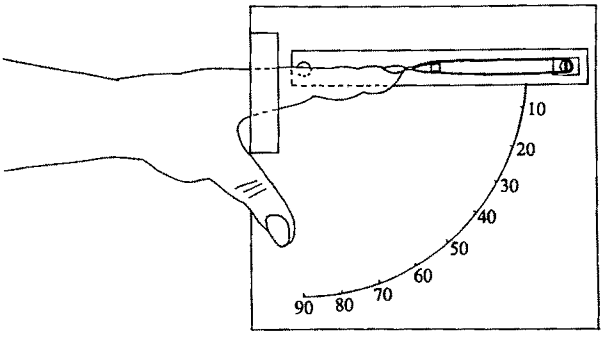

FIG. 5. Arrangement for measuring passive flexions and extensions of index. Reproduced, by permission, from Moberg (1972) (*see text*)

rested on a soft surface below the measuring table. A moveable lever, to which the finger tip was attached by a rubber band sewn to the nail and attached to a handle at the free end of the lever, permitted the experimenter to flex or extend the finger to any desired angle. This passive movement occurred almost exclusively at the proximal interphalangeal joint. The angles were read on the scale. Information from vision and sound was excluded. In some experiments the distal end of the digit was locally anaesthetized to exclude any interference from the surroundings of the nail. However, this never made any difference.

The lever was moved a few times back and forth by the experimenter before the subject was asked to estimate the angle. Each movement took 2 to 4 s and estimation of the new angle followed some 5 s later. Attempts with 2 to 3 times slower or more rapid movements gave the same results. As with the thumb experiments the experiments were preceded by training with visual guidance.

The results of the positioning tests are given in Table 2. They show that the impairment of position sense which results from blocking of all inputs from skin, joint and muscle lying distal to the wrist is not increased when anaesthesia of the cutaneous sleeve of the forearm is added to the distal blockade. Passive (or active) flexion and extension of the index within the limits used do not cause movements of the skin which covers the bellies and tendons of its long muscles in the forearm, as for movements of the thumb.

From the results of the experiments with active movements of the thumb it is postulated that information from cutaneous receptors in the forearm, activated by displacement of the skin due to the play of tendons and muscle bellies, may provide crude position sense.

TABLE 2 PASSIVE POSITIONING OF INDEX FINGER WITH AND WITHOUT DIFFERENT LEVELS OF CUTANEOUS ANAESTHESIA LONG MUSCLES UNIMPAIRED IN ALL EXPERIMENTS

			Error			
		No. of	*Maximum*			
Subject		*obs.*	*Neg.*	*Pos.*	*Mean*	*SD*
1	No anaesthesia	35	10	20	5	6
2		68	20	20	−2	8
3		80	20	20	0.4	7
1	* *See below*	27	80	10	−23	23
1	Anaesthesia from wrist	26	80	10	−31	24
2	level distally; volar	40	70	50	−8	30
3	and dorsal aspects	40	30	40	5	18
1	Added anaesthesia of	53	80	10	−29	21
2	whole forearm	40	70	50	−17	30
3	cutaneous sleeve	40	60	60	−0.5	27

* In this experiment the median nerve and dorsal radial branches were anaesthetized at wrist level, but *not* the ulnar nerve. Accordingly the palmar branch of the median nerve was left without anaesthesia, which means that the sensory field over part of the thenar and over the flexors of the index and middle finger retained sensibility down to metacarpophalangeal joint level. Such anaesthesia is difficult to obtain and will last only a short time as the anaesthetic will soon spread to this branch. This experiment was therefore not repeated.

The Gelfan-Carter Experiment

Gelfan and Carter (1967) originally reported that elongation of individual muscles by pulling the exposed tendons was not perceived. They concluded that there is 'no muscle sense in man'.

This experiment has been repeated by other workers (Moberg, 1972; Matthews and Simmonds, 1974; Matthews, 1977) with totally divergent results. Moberg confirmed Gelfan and Carter's results, but the other investigators found that the subjects recognized the pull as finger movement. Matthews (1977) stated: 'It verges on the ridiculous for there to be any doubt over the facts in such a simple experiment' and McCloskey (1978) concluded: 'Clearly this simple and important experiment must be repeated for it promises a direct and decisive answer to the question of the sentience of muscles'. Gelfan and Carter wrote that some patients reported 'pulling and movements of the skin overlying the stretched muscles', but the authors did not analyse the role of the skin. They never described the experimental details, and I have made the same omission myself. Perhaps the experiment is not as simple as was believed, and it is therefore necessary to describe the experimental procedure in detail. Our observations were made on patients with typical median nerve compression in the carpal tunnel, with their informed consent. A few case reports will therefore follow, the first including all technical details. More than 50 cases have been investigated.

Case 1. The patient was a woman of 58 years, calm, alert and healthy but for symptoms of median nerve compression, which disturbed her sleep but caused no sensory deficit in the daytime and no wasting of the thenar muscles. No premedication was used. Two per cent lignocaine with adrenaline was injected at wrist level to induce cutaneous volar anaesthesia which extended 5 cm proximally. It included the palmar branch of the median nerve but not the main nerve trunk. This means that all digits retained normal sensibility. A bloodless field was maintained by an aircuff around the upper arm. This can usually be tolerated for 20 to 25 min without disturbing pain. The experiments were always completed within the first 10 min.

The carpal tunnel was opened by an S-shaped incision running transversely just over the wrist crease. The flexor tendons (fig. 6), if necessary freed from synovial tissue over a few cm length, could now be gently grasped without any reaction. One of the flexor tendons was transfixed with a small needle and a fine thread looped around it as in the figure. In this way the tendon could be pulled distalward as well as in the proximal direction. Different tendons could be rapidly tested. A scale was fixed close to the margin of the incision. The digits were generally slightly more flexed than is shown in the figure. The position of the wrist and the digits is very important. If they are in a straight line with the forearm the major part of the muscular extensibility is already used up and only some 5 to 8 mm can be pulled out before a 'stop' is felt. Obviously the range of anatomical extensibility can vary from one individual to another. The important point in such experiments is to impose on the individual's fingers an initial degree of flexion that will allow one to pull out the flexor tendons over a sufficient distance before coming up against the 'stop'. Beyond the 'stop', perceptions aroused purely by lengthening of muscle and tendon cannot be distinguished from those aroused by deformation of the skin and fascia overlying them. If the digits and the wrist are in almost full flexion, a tendon of flexor digitorum superficialis can be pulled out about 40 mm before this 'stop' occurs. With the fingers and wrist in the position described for Case 1, somewhat less than half of the total extensibility was already used up; the rest, some 25 to 30 mm, was still available in the forearm proximal to the anaesthetized region.

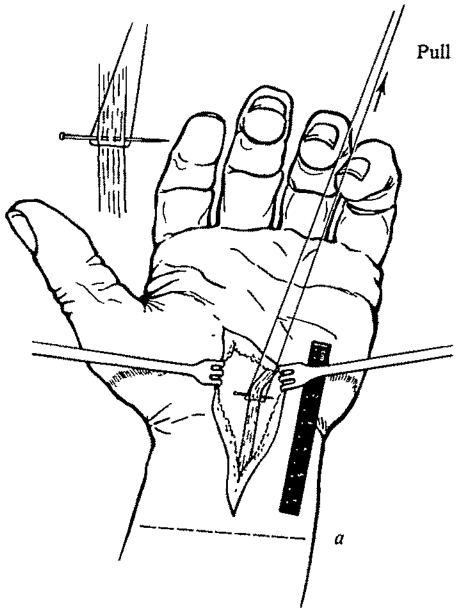

FIG. 6 Experimental arrangements in the Gelfan-Carter experiment. *a* = proximal level of anaesthesia

In about half the experiments, the flexor tendons were pinned to the bottom of the carpal tunnel by another straight needle (not shown in fig. 6) in order to immobilize the distal parts of the tendons and prevent them from moving the joints. This was necessary only if the subject reported any sensation when the tendon was pulled.

There is no doubt that the wording of the questions is important. I always ask the subjects to report if they feel anything at all in the fingers, the hand or the arm. Subjects should not be asked to state whether anything they feel is referable to muscles, tendons or joints, which are, of course, outside normal experience. In every experiment, the subjects' alertness and the reliability of their reports was controlled every two or three minutes by touches to unanaesthetized parts of the skin or by small passive movements of a finger joint.

Under all these conditions the afferents from the muscles and tendons in the forearm must have been intact. In Case 1, a longitudinal pull of a tendon in a proximal direction, causing only 2 to 3 deg of flexion of a digit, was immediately reported as flexion of the digit in question. But a pull in the distal direction, bringing more tendon out into the wound, could be performed without any reaction whatsoever. As much as 20 mm of the superficialis tendon could be pulled out, which implies a corresponding elongation of the muscle. The pull was performed without any jerks and to bring out this length took about 2 to 3 s. The displacement of the tendon was repeated in both directions 4 to 5 times with a pause of about half a minute between each trial. But when the pull was extended to almost the maximum length possible, 25 mm on the scale, the subject reported that the ring finger was *extended.* The finger was of course not moved at all, but well proximally in the forearm it was visible that the skin and fascia were pulled down in a groove, presumably evoking effective activation of cutaneous receptors in this region. The same test was repeated with the superficialis tendon to the little finger, which had a diminutive muscle belly. It was later confirmed that the muscle existed and that it could flex the little finger at the proximal interphalangeal joint. In this test I was unable to see any deformation of the skin over the small muscle, and the subject could not describe what had happened, only that something had changed. The total length of tendon which could be pulled out at that moment was 16 mm.

Case 2. A 46-year-old woman with a carpal tunnel compression of the median nerve without sensory loss. She was calm and co-operative. There was no premedication. The technique was the same as described for Case 1 with the exception that here the median nerve trunk was also blocked at wrist level. Volar sensibility in a little more than the ulnar half of the fourth finger and the whole of the fifth finger was unimpaired, together with most dorsal sensibility of the hand and fingers. The superficialis muscle to the fifth finger was present.

First it was tested that a few mm pull on the distal part of the superficialis tendon to the fifth finger, producing a few degrees of flexion, was adequately reported. Then the pull in the opposite direction was applied and 20 mm tendon was pulled out, of course with the finger position unchanged. Nothing was reported by the subject and I could not see any deformation of the skin over the minute muscle belly. The term minute is based on the very tiny size of the tendon. Not even when I felt the 'stop' when the extensibility was fully used up was there any report from the patient. The test was repeated four times.

Then the superficialis tendon to the fourth finger was tested. First, when 25 mm tendon was pulled out and a hard resistance was felt (the 'stop'), the subject reported that the finger had *extended,* which, of course, it had not. The skin region overlying the proximal part of the muscle was then anaesthetized, without influence on muscle power. Afterwards it was necessary to pull very hard to get the subject to report anything at all and she could no longer tell what had happened. In repeated tests she had no feeling of finger extension.

Case 3. A 37-year-old woman. Conditions were the same as in the two cases above with the difference that the whole volar forearm cutaneous sleeve was anaesthetized as far as the medial condyle of the elbow. At wrist level cutaneous anaesthesia only was used; the median nerve was not blocked for the nerve surgery until after the test. Full muscular power was unimpaired. The index superficialis flexor could be pulled out as far as the 'stop', 20 mm, without any report from the subject. The same was the case with the superficialis to the little finger. If the fourth finger was maximally flexed the superficialis could be pulled out 40 mm without the subject reporting anything. This was also repeated several times.

Case 4. A 29-year-old woman with very slender muscles. Without premedication, local volar infiltration anaesthesia to 5 cm above wrist level was combined with a median nerve block at wrist level. In this case the fingers and the wrists were placed in so much extension that the superficialis of the fourth finger could only be pulled out 10 mm before the 'stop' was reached. Small rapid jerks were applied with an amplitude of 2 to 3 mm and repeated 2 to 3 times a second. No upper forearm anaesthesia was administered. The jerks were continued with more and more tendon slowly brought out in the wound. The subject reported nothing until about 8 mm muscle elongation had taken place and one was very close to the 'stop'. Then she said a 'pumping' in the arm had started.

Case 5. A 40-year-old man, with strong muscles. He had somewhat more advanced median nerve compression symptoms with slight wasting of the abductor pollicis brevis muscle but no loss of hand sensibility in the daytime. In this case, again with no premedication, cutaneous anaesthesia was applied from wrist level as far as 2 cm proximal to the elbow. All long muscles had full power. The digits were placed in such a position that 40 mm of the superficialis tendon of the ring finger could be pulled out before the 'stop' was felt. The subject did not report any sensation, either in response to the 40 mm pull or when the pull was slowly made stronger until the thread broke (at a pull of 1.8 kg).

Case 6. A nurse aged 42 years, calm and co-operative. with symptoms of the carpal tunnel syndrome at night. Without premedication, local subcutaneous anaesthesia was established on the volar surface extending from 5 cm proximal to wrist to middle of palm (palmar branch of median nerve). Ulnar innervation was intact. For these observations the palm was in line with the forearm and the fingers held straight. The tendons were those of flexor digitorum superficialis to the middle and little fingers. From this initial position the former tendon could be extended only 5 mm before the 'stop' was felt, the latter tendon a little less. The tendons were not forcibly extended beyond these limits. The subject always reported spontaneously that one or other fingers had been extended. However, when the fingers were semiflexed so that 15 to 20 mm of tendon could be pulled into the wound, the subject reported nothing, even when directly questioned. The tendons were transfixed and pinned to the floor of the carpal tunnel so that no movement was imparted to the fingers. The tendons were never slack—the muscles retained their tone. As little as 1.0 mm pull in the opposite direction was always reported correctly as finger flexion. The subject had been told nothing about the experiment except that it was to test what she was able to feel in the arm and hand under different conditions.

Personal observations. This experiment was performed on the author by his successor as Head of the Department of Hand Surgery, Dr S. Edshage. Subcutaneous volar anaesthesia covered a 6 cm broad band just proximal to the distal wrist crease, leaving sensibility intact on the entire palm and volar surface of the digits and the muscles and tendons unaffected. Eight ml of 1 per cent mepivacaine was injected. No tourniquet was applied. A curved 4 cm incision gave access to the flexor tendons. There was of course no indication to divide the carpal ligament. The superficialis tendons to the index finger and middle finger and the well-developed palmaris longus tendon were set up as in fig 6. The following results were obtained.

1. *Fingers.* With tendon pulls at muscle lengths wholly within the normal range, and with movements between 2.0 and 10.0 mm alternating roughly sinusoidally between 0.3 and 1.0 Hz, the subject reported no sensation. In several tests these limits were exceeded without any sensation being reported. Two mm excursions of the superficialis tendons in the centripetal direction gave about 10 deg flexion of the proximal interphalangeal joints, 5 mm gave about 30 deg and 10 mm about 70 deg.
2. With larger centrifugal pulls which reached the 'stop', or smaller pulls, starting nearer the limit so that they too reached the 'stop', the subject reported sensations proximally in the forearm. Sometimes the experimenter could observe at those moments a slight movement of skin proximally in the forearm. The consciousness of finger extension in this situation—there was never any feeling of finger flexion—seemed to the subject as much an interpretation of what was felt as a direct signal from moving fingers. The experimenter of course saw that the digits were lax and immobile. The subject could not distinguish between pulls of the superficialis tendons of the index and the middle fingers.
3. The slightest centripetal pull, flexing a digit only a few degrees, was immediately reported as coming from the correct digit and from its proximal interphalangeal joint. The subject could tell the experimenter that he was working on the superficialis tendon of index even before he had identified it in the wound. Later, when the experimenter thought, correctly, that the subject was expecting a pull on the ring finger, he tested the index finger instead, and was immediately told that it was now the index. The overwhelming difference between the quality of the sensation obtained from centripetal pulling and the occasional vague sensation from pulling in the other direction, where little movement of the skin occurred, must be stressed.

4. Centrifugal pulling on the palmaris longus tendon was reported as a sensation proximally in the forearm. Centripetal pulling was reported as a slight broad pressure in the palm (of course due to the palmar aponeurosis).

Comment. The observations on these six (and on many other) cases, and in the healthy volunteer, support the working hypothesis put forward in the preceding section. It is postulated that when a flexor muscle is stretched in the range close to its maximum physiological length by a pull on the tendon, then activation of cutaneous receptors by deformation of the skin and subjacent fascia of the forearm may be perceived by the subject as extension of a finger. In all experiments, when the deformation of the skin was negligible or when activation of cutaneous receptors in the forearm was prevented by anaesthesia, no sensation was evoked when a single muscle was stretched. Similar findings were made if a steady slow pull was exerted or small rapid stretches were used. It seems likely that the information from distant cutaneous receptors can be an important source of error in experiments on muscle sense.

CONCLUSIONS

A variety of clinical observations relating to the hand suggests that information from muscle receptors cannot alone provide kinaesthesia in either passive or active finger movements. Reinvestigation of the effect of pulling a tendon during surgery confirmed the original report (Gelfan and Carter, 1967) that impulses in muscle stretch receptors alone do not arouse sensation. However, stretch beyond the physiological length of the muscle causes a displacement of the skin overlying the muscle, which can give rise to the sensation of a finger movement in the direction which, if actually occurring, would elongate the muscle.

Experiments with active positioning of the thumb in normal subjects after nerve block and cutaneous anaesthesia at different levels suggest that cutaneous receptors in the forearm activated by the play of tendons and muscles may provide crude position sense for the fingers.

Finger kinaesthesia may depend on cutaneous and/or joint receptors and some clinical observations are reported which favour the role of the former rather than the latter. Since distant cutaneous receptors were found to contribute, it seems overwhelmingly likely that the more strategically placed cutaneous receptors in the fingers play an important role in kinaesthesia. This view is supported by recent findings showing that many cutaneous receptors in the hand are activated during movement of a finger even if no object is touched (Vallbo and Johansson, 1978).

The studies reported in this paper and those in the companion paper by McCloskey *et al.* (1983) have had different objectives. The latter seeks only to discover whether stretching of muscles by pulling tendons (the Gelfan-Carter experiment), or stimulation of muscle spindles by longitudinal vibration of tendons, can arouse sensations of movement without any coexcitation of inputs from skin and joints.

My first objective has been to show that in the totality of kinaesthetic function, particularly of the hand, the cutaneous afferents are of great, probably leading importance. In practical reconstructive surgery the preservation of cutaneous innervation where it remains undamaged, or the transfer of innervated skin to moving parts from which the normal cutaneous innervation has been lost, has been found to be essential; it has been found that an intact input from the muscle spindles cannot substitute for it. And in the rehabilitation of the hand after surgery, successful training in the use of the grip depends on conscious attention to the sensations aroused by movements. Thus successful rehabilitation has been found to depend on the presence, at the working surfaces, of innervated skin.

My second objective has been to show that in experimental work on sensations aroused by pulling on exposed tendons, undetected coexcitation of cutaneous afferents must be recognized as an important source of error—by traction on skin overlying muscle bellies which arise in part from the deep fascia, by raising of the skin overlying pulled tendons, or by stimulation of the skin by frictional drag from sliding tendons acting on its deep surface.

McCloskey *et al.* (1983) state (p. 34) that in their Gelfan-Carter experiments, when the wrist and digits were in the 'O' (straight) position, extension of the wrist would extend the digital flexors a further 1.0 to 1.5 cm. However, as measured at operation as well as calculated from anatomy, no more than a further 0.6 to 0.8 cm is possible in a large male hand, for most hands less. This is near the point at which the 'stop' is felt when the tendon is pulled further. Thus (*see above*, Cases 1, 2, 4 and 6) the complicating cutaneous factor is already present, and the experiment is no longer a pure muscle-lengthening one. In my own observations, the results obtained with palm and fingers in line with the forearm differ totally from those obtained when the initial length of the muscle is less, and the reserve available for pulling out is correspondingly greater.

In the experiments on myself, the striking feature was the overwhelming difference in quality between the clearcut awareness of finger flexion in response to a centripetal tendon pull causing a few degrees of finger flexion, and the crude sensation of finger extension evoked by centrifugal pull when the reserve length of the muscle was fully used up, as in the experiments of McCloskey *et al.* (1983).

McCloskey *et al.* (1983) discuss the cutaneous factor as a possible source of error, but I cannot find that they have excluded it experimentally by anaesthetizing sufficient areas of skin. This also seems important in the experiments on McCloskey's big toe, and in the vibration studies as well as the pullings. Matthews and Simmonds (1974) could not obtain effects when vibration was used directly on tendons.

In conclusion I wish to stress once again the practical importance of exact knowledge in this field for major reconstructive surgery of the limbs and for rehabilitation, and to acknowledge gratefully the important part played by my friend Ian McCloskey in bringing my work to the point of publication. Without his superb review of the literature (McCloskey, 1978), and the several years of stimulating correspondence with him, some of my experiments would never have been performed.

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SENSORY EFFECTS OF PULLING OR VIBRATING EXPOSED TENDONS IN MAN

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SUMMARY

The role of muscle receptors in proprioception has been demonstrated in a variety of ways (for review *see* McCloskey, 1978) but is still doubted by some. One simple but critical experiment has produced conflicting results: when a tendon of a conscious subject is exposed at operation under local anaesthesia, and pulled so as to stretch its muscle while the joint at which the muscle acts is held still, the subject is claimed by some to perceive nothing (Gelfan and Carter, 1967; Moberg, 1972), while others claim that the subject feels that the joint seems to move (Matthews and Simmonds, 1974). In the present study 4 patients were studied while undergoing surgery at the wrist or hand under local anaesthesia, and a more extensive study was carried out in the laboratory on the exposed, transected tendon of *extensor hallucis longus* of one of the authors (D.I.McC.). All 4 patients and the experimental subject detected stretches imposed on their muscles, and reported them as rotations of the joint or joints to which those muscles attach. In all cases the movements reported were in the direction of joint rotation that would normally stretch the muscle tested. In the experimental subject it was shown that stretches were detected with comparable acuity to that demonstrable for the detection of movements imposed on the intact toe. Also, the subject was able to detect, as joint movements, sinusoidal stretches of less than 1 mm imposed on the tendon at 1 or 5 Hz.

The experimental subject experienced illusory movements of plantar flexion of the big toe when longitudinal vibration at 100 Hz, 20 to 100 μm amplitude was applied. These were sometimes partly masked by spread of the vibration through the foot. These vibration-induced illusions correspond to those reported by Goodwin *et al.* (1972) for transverse vibration applied through the skin.

The subject could maintain a constant tension through the tendon in a contraction in which his effort was held constant. If, during such an effort, a downward movement was imposed on the toe to which the tendon normally connects, or the skin on the bottom of the toe was scratched, achieved tension fell.

INTRODUCTION

This paper seeks to answer the questions: can pulling or vibrating the tendon of a muscle in an awake subject, without moving the joint to which that muscle attaches, give rise to sensations of joint movement? If so, can the extent of the disturbance necessary to elicit such sensations provide an indication of the receptors responsible?

Until about ten years ago conventional physiological opinion held that muscles

P 25688

are insentient, that the discharges from intramuscular receptors are involved in important but unconscious reflexes, and that proprioceptive, or kinaesthetic, sensations arise only from the discharges of receptors in the joint capsules and ligaments. While this view is still held by many physiologists, powerful evidence has steadily accumulated against it, and in favour of the view that kinaesthetic sensibility is based upon the discharges from receptors in joints, muscles and skin (for reviews, *see* Goodwin *et al.*, 1972; Goodwin, 1976; Matthews, 1977; McCloskey, 1978; Burgess *et al.*, 1982).

An important experiment reinforcing the former view that muscles are insentient was carried out in 1967 by Gelfan and Carter. These investigators pulled on the tendons of patients undergoing surgery at the wrist or ankle under local anaesthesia. They found that when the tendons were pulled so that forces were exerted only distally, thus flexing individual digits while shortening the resting muscle length, the subjects 'readily recognized and localized the joint movements'. However, when the tendons were pulled in the opposite direction, stretching the muscles but without moving the joints, 'at no time did any of the subjects experience any sensation referable to the muscles', although some reported 'pulling or movement of the skin overlying the stretched muscles' and various sensations at the site of skin incision. The extensions imposed on the muscles were as great as 5 cm, achieved in 1 s. What was not said by Gelfan and Carter (1967) was whether muscle pulls gave any sensations *referable to the joints* usually moved by those muscles. Indeed, it seems possible that the subjects were asked only about detecting 'length and tension changes' of the muscles, and that they were not asked about specifically proprioceptive sensations.

It is now known that when an entire joint, including, presumably, its complement of joint receptors, is removed and replaced by a prosthesis, good proprioceptive acuity remains (Goodwin *et al.*, 1972; Moberg, 1972; Cross and McCloskey, 1973; Grigg *et al.*, 1973). If the cutaneous and joint receptors in a digit or in the whole hand are locally anaesthetized, leaving available for proprioception only the receptors in flexor and extensor muscles which lie outside the anaesthetic area, proprioceptive sensations remain, although acuity is considerably blunted (Goodwin *et al.*, 1972; Gandevia and McCloskey, 1976). In the latter case, the loss of cutaneous receptors has been taken to be responsible for the reduced (but not abolished) proprioceptive sensibility, and to indicate an important proprioceptive role for cutaneous receptors in the digits (for example, Gandevia and McCloskey, 1976; McCloskey, 1978). The contributions from cutaneous receptors at other joints may be less, however, because it has been found that if local anaesthetic is introduced into the capsule of the knee joint, and a sleeve of skin around the joint is locally anaesthetized, proprioceptive acuity is unaffected (Clark *et al.*, 1979).

These findings indicated a role for muscle receptors in proprioceptive sensation, and made it necessary to repeat the tendon-pulling experiment of Gelfan and Carter (1967). This was done by Moberg (1972) and by Matthews and Simmonds (1974). Both studies were carried out in patients undergoing surgery at the wrist under local anaesthesia. Moberg (1972) gave very little detail of his experiment, but reported that 'a hard pull which has its effect proximally on the normal muscles and tendons does not give any conscious sensation at all'. This was a more general conclusion than that of Gelfan and Carter (1967), as it is clear that Moberg had proprioceptive sensations in mind and not just sensations referable to the muscles. Matthews and Simmonds (1974), however, disagreed. They studied 5 patients, held the hands 'in moderate flexion', pulled the tendon to and fro with fine forceps so as to stretch its muscle without moving the relevant digit (movement about 5 mm at 2 Hz) and found that 'without exception the subjects then reported "you are moving my finger" (or thumb) and allocated the movement to the correct digit'. In advocating further study of this question, Matthews (1977) later observed, 'it verges on the ridiculous for there to be any doubt over the facts in such a simple experiment'.

The conflicting results reported for the tendon-pulling experiment were all obtained in patients at operation. Clearly, however, the operating room is not entirely suitable for experimentation: the patient may be anxious and distracted, considerations of patient-care necessarily limit the time available for experimentation and there are limitations on the extent and reliability of controls and measurements which may not exist in the physiological laboratory. Furthermore, as in most experiments, it is likely that an observer has expectations of a certain result. That this expectation might be detected by a patient in a situation where he is particularly dependent on those carrying out the procedure must have concerned the experimenters involved. It is therefore clearly necessary to take account of this factor in any attempt to resolve the question.

The present paper reports results from experiments on the sensory effects of pulling on tendons in conscious subjects. Results are presented from a series of patients studied at operation: here the questions of apprehension and expectation on the part of both patient and observer were given particular attention. The findings on the patients are confirmed and extended by results obtained in a more extensive experiment carried out in the physiological laboratory. Here the subject was one of the authors (D.I.McC.), who has many times argued a case for one side of the question at issue, and this imposed stringent requirements on the experimenters to perform the study under such carefully controlled conditions that the subject's prejudices could not influence the results.

METHODS

Patients

The patients were examined during surgery carried out under local anaesthesia on the wrist or hand. Sensory testing was performed by the surgeon (R.H.), who can be considered an unbiased observer. His cooperation had been achieved through approaches by D.I.McC. by letter and by telephone, but the two had not met until the morning on which the operations were performed. When enlisting his participation, he had been sent the conflicting accounts summarized in the Introduction, as background. All the sensory testing to be described was carried out by R.H., with D.I.McC. standing in the background making notes, not introduced to the patients, and taking no active part in the procedure. Research and experimentation were not mentioned: the patients were advised only that sensation would be checked as the surgery proceeded, and gave their consent to this. The sensory tests lasted 3 to 5 min and did not significantly prolong the operations, or cause the patients any discomfort. No specific mention of finger movements was made prior to or during the operation. Efforts were made to avoid setting any expectations for the patients so that there could be no question of their seeking to meet such expectations. Details of the procedures carried out on each patient are given in the Results.

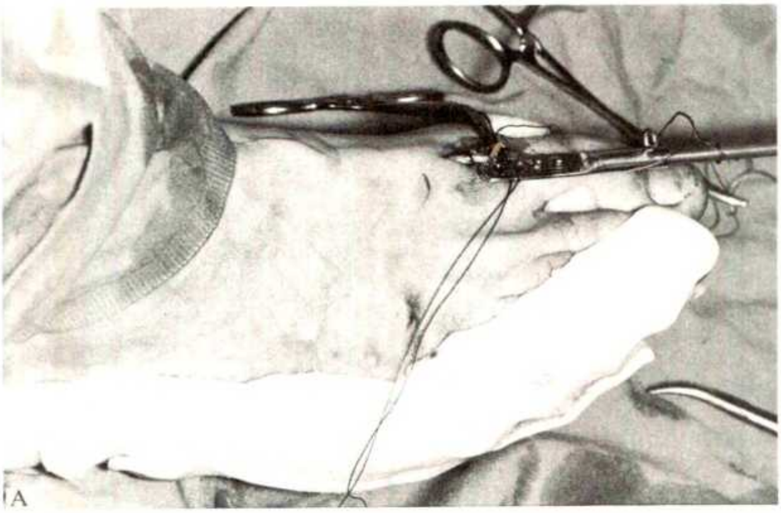
Volunteer Subject

More extensive observations were made on one of the authors, D.I.McC. He was seated throughout the experiment in a comfortable armchair placed on a table. Both feet rested on the table top. The right foot was placed into a closefitting, rigid cast ('Aquaplast') specially moulded to fit the experimental foot. The cast ran from behind the heel, across the sole, and folded around each side of the foot and over the 2nd to 5th toes (*see* fig. 1). A firm extension of the cast wrapped around three sides of the proximal phalanx of the big toe, preventing all movement at the metatarsophalangeal joint. The remaining toes were immobilized at an angle of about 45 deg in dorsiflexion by the cast. Movement at the interphalangeal joint of the big toe was not restricted by the cast, but provision was made for fitting a long nail into the cast along the plantar surface of the toe, so that this joint could be immobilized by tying the distal phalanx of the toe to the nail. The cast was clamped firmly to the table top. Lignocaine (2 per cent, 10 ml) was infiltrated under the skin on the dorsum of the right foot, anaesthetizing a roughly circular area of skin about 6 cm in diameter, with its centre over the metatarsophalangeal joint of the big toe: in the toe itself, only the skin at the base on the dorsum, no closer than 2 cm proximal to the interphalangeal joint, was anaesthetized. Using aseptic surgical technique, the tendon of *extensor hallucis longus* was exposed through a longitudinal incision about 3 cm long at the level of the metatarsophalangeal joint. At this stage the tendon was marked and the interphalangeal joint was moved through its full range of excursion: measurement of the angular excursion and displacement of the tendon showed that 70 deg rotation corresponded with 7 mm of tendon movement. With the muscles completely relaxed a mark was made on the skin beside the mark on the tendon to locate the resting position of the muscle.

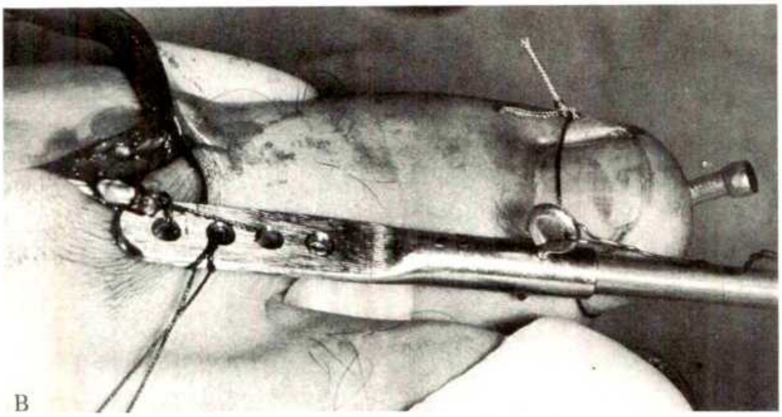
This resting length of the muscle was not its minimum physiological length, as it could shorten a further 3 mm by active dorsiflexion—the 7 mm range studied was from full dorsiflexion to full plantarflexion. Futhermore, the plane of the foot made an angle of ~120 deg with the leg when the ankle was positioned as it was throughout this study, but the subject was capable of active dorsiflexion of the ankle to ~60 deg, which could further reduce the length of *extensor hallucis longus*.

The tendon was then cut and its proximal end was stitched to a sterile metal fitting connected to a brass rod. The other end of the rod was attached to an electromagnetic vibrator driven by a ramp generator (Advanced Dynamic Industries: Vibrator AV-50 and amplifier N-300). The vibrator operated with position feedback, and had previously been calibrated at a range of loads. Signals of position and tension were available and were led to an oscilloscope and a pen recorder.

FIG. 1. Photographs show the experimental arrangement used in the experiment on D.I.McC A shows the foot encased in a rigid cast, making movement possible only at the interphalangeal joint of the big toe The tendon of *extensor hallucis longus* has been exposed, transected, and stitched to a rod, the other end of which is attached to an electromagnetic vibrator. During the experiment, the cast was clamped to the tabletop, immobilizing the foot. B shows a closer view of the tendon attachment. It also shows how the distal phalanx of the big toe was immobilized by tying it to a nail which ran along the plantar surface of the toe and was embedded in the cast. C shows tendon attachment. Note also that extensions of the cast wrap up from the sole around the sides of the proximal phalanx of the toe, preventing movement at the metatarsophalangeal joint: this is visible in all three panels.



A



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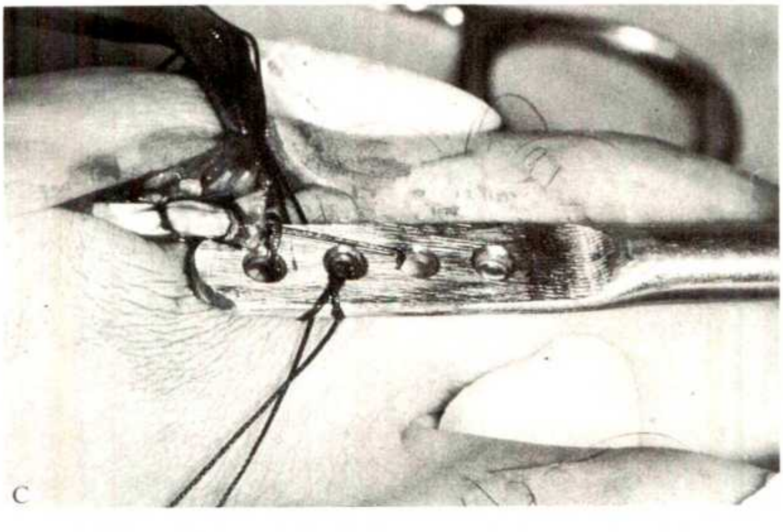

C

The subject could see neither his foot nor the recording apparatus. The experimenters who operated the equipment made their adjustments to it out of the subject's view. No sounds accompanied the operation of the electromagnetic vibrator, except during its generation of high frequency (50 to 400 Hz) sinusoids at higher amplitudes (50 to 200 μm), when a faint buzz was just audible. The subject was not informed about his performance, either directly, or indirectly through conversation between the experimenters.

Experimentation lasted for approximately 2¼ h, after which the tendon was disconnected from the apparatus, its ends sutured together and the wound closed. Recovery of power and range of movement was complete within several weeks.

RESULTS

Observations on Surgical Patients

All 4 patients volunteered that they felt movements of the digits when the forearm muscles were stretched by pulling on appropriate tendons in such a way that the hand and digits were not actually moved.

Case 1, C.M. A 59-year-old woman. Operation for 'trigger thumb' on right side, under local anaesthesia (local infiltration of lignocaine at base of thumb over the proximal phalanx and thenar eminence); bloodless field achieved by inflation of sphygmomanometer cuff to 300 mm Hg above elbow; observations made 10 min after cuff inflation. The tendon of flexor pollicis longus was grasped in a pair of forceps and pulled and released gently through 0.5 cm at about 1 Hz within its sheath. The distal end of the tendon was immobilized by a second pair of forceps, and the thumb was held in full extension by the surgeon's assistant. The back of the hand and forearm lay flat on the table with the wrist straight. The patient's vision of the operative field was blocked.

'Do you feel anything?'
'I feel my thumb moving.'
'What joint of your thumb?'
'The end one.'
'Show me.' (Patient holds up other hand, moves terminal joint back and forth at about 1 Hz, through 45 to 60 deg.)

Individual pulls on the tendon were perceived as extension movements of the thumb. Static position sense was not tested.

Case 2, L.L. A 34-year-old man. Operation to relieve median nerve compression under local anaesthesia (local infiltration of lignocaine at volar surface of wrist) on left side; bloodless field achieved by cuff, observations made between 9 and 12 min of cuff inflation. The patient could not see the operative site. He was heavily sedated, and slept through most of his operation. He was roused for sensory testing. The tendon of *flexor digitorum profundus* to the index finger was grasped with forceps, as before, and moved gently back and forth through 0.5 cm at about 1 Hz. All the fingers were fixed manually in full extension by an assistant. Again, the wrist was straight. The patient was asked if he felt anything and immediately replied that his finger was being moved. When asked which finger, he held up the opposite hand and moved the index finger back and forth in an action like pulling a trigger: this involved flexion and extension at distal and proximal interphalangeal joints, plus slight movement at the metacarpophalangeal joint. When asked what part of the left index finger was bending, he indicated the full length of his index finger by running his thumbtip back and forth along the finger on the indicator side. When the imposed displacements were made at the same velocity, but with pauses between the pull and release components, the patient indicated that each pull was sensed as an extension of the finger.

Case 3, N.S. A 56-year-old man. Operation to relieve Dupuytren's contracture on left side; local anaesthetic blockade of radial, median and ulnar nerves at wrist; bloodless field achieved with above-elbow cuff; observations made between 14 and 19 min of cuff inflation. Patient could not see the procedure. Tendons to the ring and little fingers were pulled as before, with fixation of the wrist and distal fixation of the fingers as before. This patient readily identified pulls of ~0.5 cm, as finger movements when the *superficialis* and *profundus* tendons to the ring finger were pulled. He correctly identified the appropriate finger, and nominated the distal interphalangeal joint as extending when the *profundus* was pulled, and the metacarpophalangeal and proximal joints as extending when *superficialis* was pulled. He reported no sensation when the *sublimis* tendon to the little finger was pulled, even for larger pulls (~ 1 cm). When *profundus* to the little finger was pulled he reported no sensation for the 0.5 cm pulls, but for 1 cm pulls reported a slight extension of the terminal joint of ring finger. Inspection revealed clear movement of the ring finger *profundus* tendon occurring at this time (the tendons to the two fingers are joined proximal to the point where traction was applied). Voluntary flexion of the little finger was impaired, and at one test absent, at the time of testing. The loss of motor power and muscle sensation for the little finger in this patient could have been due to the local anaesthetic tracking proximally into the flexors of the little finger, or significant ischaemic/pressure block of the nerves to these muscles by the cuff (note: observations made 14 to 19 min after cuff inflation).

Case 4, G.A. A 52-year-old man. Removal of granulomatous lesion on right palm under local anaesthesia (infiltration of lignocaine under lesion). Bloodless field achieved with cuff, observations made between 8 and 11 min of inflation. The tendon of *flexor digitorum profundus* to the little finger was exposed in the palm and pulled upon. Fixation of the wrist and of the fingers distally were as before. Pulls at ~ 1 Hz, of about 0.5 cm amplitudes were first tried. The patient reported feeling that his ring and little fingers were moving, and that his wrist was also being slightly flexed and extended. He indicated this by movements of his opposite hand in time with the imposed pulls: these movements involved extension of metacarpophalangeal and both interphalangeal joints of ring and little fingers with each pull, and flexion of the same joints with each release. These indicator movements also involved slight (~ 10 deg) extensions and flexions of the wrist. For larger imposed pulls (~ 1 cm) on the same tendon, the patient reported clear movement of the little finger, and indicated this with an extension on the indicator side similar to the previous one, but with the excursion of the little finger alone greatly accentuated. In this patient, the operative incision did not permit a view of other tendons, so it could not be confirmed that movements imposed on the tendon to the little finger were transmitted to the tendon of the ring finger. However, the normal connections between the two make this likely, and the findings on sensory testing also suggest that it occurred.

Laboratory Experiment

Description of sensations. The subject could readily detect movements manually imposed on the interphalangeal joint of the big toe after its extensor tendon was cut. The imposed movements were not measured, but were of the order of 10 to 30 deg made within 1 to 2 s. Movements in both directions were detected.

When the interphalangeal joint was immobilized, the subject could detect displacements imposed on the muscle through the proximal end of the cut tendon, while his muscles were relaxed. These detections were measured in several ways, as described below. As the tendon was pulled either manually or by the electromagnetic vibrator, the sensation of plantar flexion at the distal joint of the toe was regularly reported. As the tendon was released, there was a sensation of dorsiflexion of the joint: this latter sensation was elicited only when the release was sudden and complete, and from a muscle length near to, or beyond, the resting length (namely, a release from a load of approx. 0.4 to 0.5 kg, the tension required to hold the muscle at resting length). Smaller or slower releases had no sensory effects. With the tendon unloaded the toe was felt to be dorsiflexed to almost its full extent. With the tendon held extended by an amount corresponding to its full excursion during maximal plantar flexion, the toe was felt to be plantar flexed. No other observations on static position were made. Sinusoidal displacements of the tendon at 1 Hz or 5 Hz were felt as to and fro movements of the toe at its terminal joint. All sensations associated with tendon pulling were clear, but were noted to be unusual because they were unaccompanied by sensations of cutaneous distortion and pressure *in* the toe itself. At the time of the experiment the sensations were described as being 'as if the toe is blowing back and forth in a breeze'.

Sinusoidal displacements. Detection thresholds were determined for sinusoidal displacements imposed by the electromagnetic vibrator. For these the subject was asked to press a marker button as soon as he felt movement of the toe and to release it when the movement ceased. He was given a spoken warning when a series of trials was to commence. An experimenter then gradually increased the amplitude of a sinusoidal displacement applied to the tendon from zero until the subject pressed the marker button, and then either continued to increase the amplitude or held it steady for a variable time (1 to 5 s). The amplitude of displacement was then reduced gradually to zero. During the reduction, the subject released the marker button when the sensation of toe movement disappeared. The whole sequence was complete within 15 to 25 s. Without further warnings, a further 3 or 4 similar trials were carried out. Similar observations were carried out from different muscle lengths and at different frequencies in the relaxed muscle. One series of trials was carried out at resting muscle length, but with the subject exerting some active tension (achieved by attempting to dorsiflex the toe). Fig. 2 shows the results obtained. Amplitudes of 0.3 to 0.5 mm were reliably detected when the muscle was loaded, and 0.6 to 0.8 mm when it was unloaded.

Ramp displacements. With the muscle relaxed and held at its resting length, ramp displacement was imposed at various velocities. Sets of 10 displacements each either pulling or releasing the tendon at the same velocity were given after a spoken warning. The subject was required to respond correctly within 3 s of a displacement—'in' when the toe was felt to dorsiflex, and 'out' when it was felt to plantarflex—to be counted as having detected a given displacement. The test displacements were increased or decreased by 0.1 mm in successive trials until the smallest displacement for which the subject could reliably detect 7 of 10 pulls was determined. Many trials were necessary and complete data were obtained only for displacements made at 2.5 mm/s (corresponding to 25 deg/s angular velocity for joint rotation). Here, the 70 per cent detection level for imposed pulls was 0.75 mm (this corresponds to 7.5 deg of plantar flexion). At the same velocity movements of 2 mm in the opposite direction were not detected. The 50 per cent detection level for pulls was 0.5 mm (5 deg). There were no false positives. Some further observations were made at 0.2 mm/s (2 deg/s). At this velocity all extensions of 2 mm (20 deg) were detected, but no displacements in the opposite direction were detected. These results are plotted in fig. 3 in terms of their corresponding angular displacements and velocities, and are compared with the 70 per cent detection levels for imposed toe rotations determined in the subject some days before the tendon-pulling experiment. In the earlier experiment the foot had been immobilized in the same cast, and the toe had been coupled to the vibrator through a pin in a large thumbstall slipped over the tip of the toe. Fig. 3 shows that the detection threshold for proprioceptive sensations induced by tendon pulling were similar to the thresholds for rotations imposed on the intact toe.

Vibration. Illusions of toe movement were induced by longitudinal vibration of the tendon. Goodwin *et al.* (1972) described illusions of joint movement induced by transverse vibration of muscle tendons through the skin, using vibration of frequency 100 Hz and amplitude of about 0.5 mm. The induced illusory movements were in the direction of joint rotation which would normally stretch the vibrated muscle. Similar vibration applied over the joint capsule induced no illusory

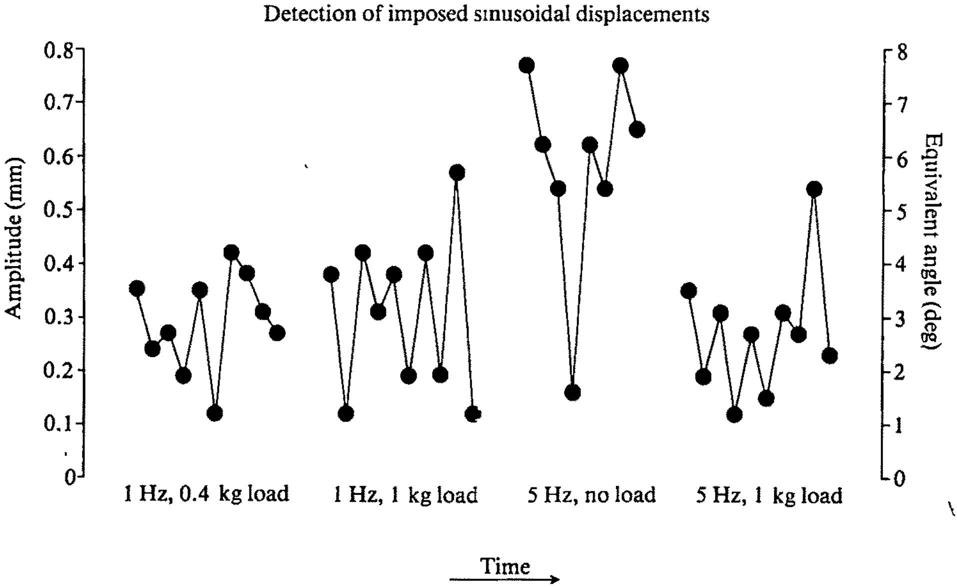

FIG. 2. This shows amplitudes of imposed sinusoidal displacements applied longitudinally to the exposed, transected tendon of D.I.McC. and detected as rotations of the interphalangeal joint of the big toe. Amplitudes are shown in mm on the vertical axis (at the *left*), and as the angular rotation of the joint to which they are equivalent in the intact toe (*right*). Four groups of data points are shown· the first was obtained with the test muscle relaxed, and held at its resting length (this required drawing the muscle out with a tension of 0.4 kg); the second and fourth were obtained with the muscle at this length and the subject adding an element of active tension; the third was obtained when the relaxed muscle was first allowed to shorten, so that there was no resting tension. In each group of points the first point was obtained when the subject first detected a gradually increasing sinusoidal displacement, and the second when he could no longer detect the subsequently decreasing sinusoidal displacement. Subsequent pairs of points in each group were obtained similarly.

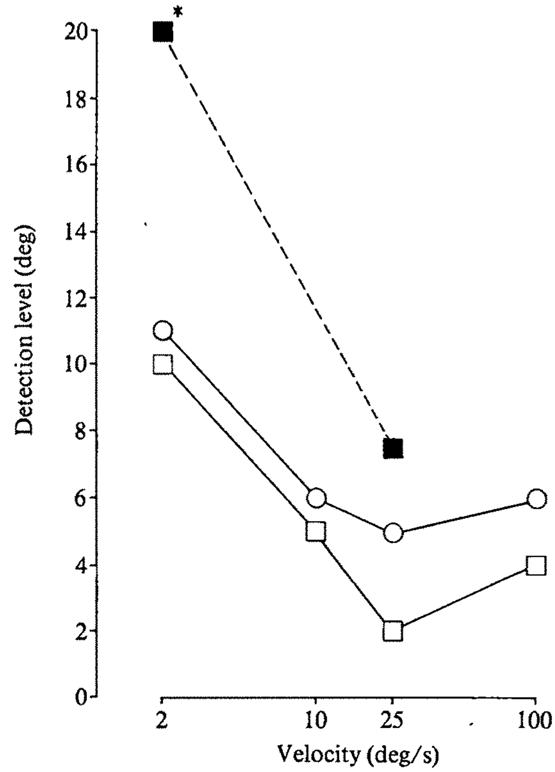

FIG. 3 This shows the relation between 70 per cent detection levels of joint rotation and the angular velocity of rotation for the interphalangeal joint of the big toe of subject D.I.McC. The open symbols show the relation for the intact toe; circles show data for imposed ramp displacements into dorsiflexion and squares for plantar flexion. The filled squares show data obtained subsequently in the experiment on the subject's exposed, transected *extensor hallucis longus* tendon. Each point represents the smallest angle (or equivalent angle) of imposed displacement, at the velocity shown, for which the subject correctly nominated the direction of joint rotation in 7 or more of 10 trials (*see text*). The point marked by an asterisk indicates 100 per cent correct detection—70 per cent detection was not determined at this velocity. Velocity is plotted on a log scale. In the experiment on the exposed tendon, ramp displacements at 2.5 mm/s (equivalent to 25 deg/s) were tested in two directions; the 'pulls', detected as plantar flexions, are plotted; 'pushes' at the same velocity, even when 2 mm (20 deg) in amplitude, were not detected.

movements. Goodwin *et al.* (1972) suggested that the illusions were caused by the excitation of muscle spindles within the vibrated muscle because it was known from animal experiments (*see* Brown *et al.*, 1967), and has subsequently been confirmed in man (Burke *et al.*, 1976), that vibration is a potent stimulus for such receptors. On this basis they proposed a role for muscle spindles in kinaesthesia. Subsequently, however, Matthews and Simmonds (1974) failed to elicit kinaesthetic sensations by vibrating the exposed tendons of patients undergoing surgery at the wrist under local anaesthesia. In these experiments, however, the vibrator was not attached to the tendon and Matthews (1977) noted later that 'it was uncertain as to how effectively the vibration was being transmitted to the muscle along the length of the tendon'. In the present experiment it was possible to apply longitudinal vibration directly to the tendon.

The vibration itself was felt as an intense buzzing sensation, like a tight sock, pressing over the whole foot. Considerable experimental time was spent attempting to confine the vibration to the tendon and belly of *extensor hallucis longus*, with little success. At higher frequencies (200 to 400 Hz) and amplitudes (100 to 200 μm) of vibration, the spread of vibration was so intense that the subject could detect no movements of the toe. Illusory movements of plantar flexion at the terminal joint of the toe were reported on many occasions, most reliably when the vibration frequency was 50 to 100 Hz and its amplitude 20 to 100 μm. Even at these levels, however, the detections remained difficult to make because of the still intense spread of vibration throughout the foot and toes.

Vibration usually elicited an involuntary contraction of the muscle whether it was initially stretched (within its physiological range), voluntarily contracted (~1 kg tension), or unloaded. The velocity of the illusory movements was registered by the subject who moved a long lever attached to a potentiometer at a subjectively equal angular velocity. The potentiometer was placed on the arm of the subject's chair with its axis parallel to the axis of rotation of the big toe, and the lever which operated it was aligned with the toe and had the same angular excursion as the toe normally had. Fig. 4 shows a recording made in this way. At faster paper speeds than shown in fig. 4 it was possible to measure the angular velocities indicated: these ranged from 30 to 70 deg/s for frequencies of 50 to 100 Hz and amplitudes of 20 to 100 μm. Other frequencies and amplitudes were not systematically studied.

Other observations. Isometric contraction of *extensor hallucis longus*, achieved by attempting to dorsiflex the toe, produced no sensation of movement. Sustained efforts gave fairly constant levels of tension. If, during such an effort, an experimenter stroked the plantar surface of the big toe with a blunt object, achieved

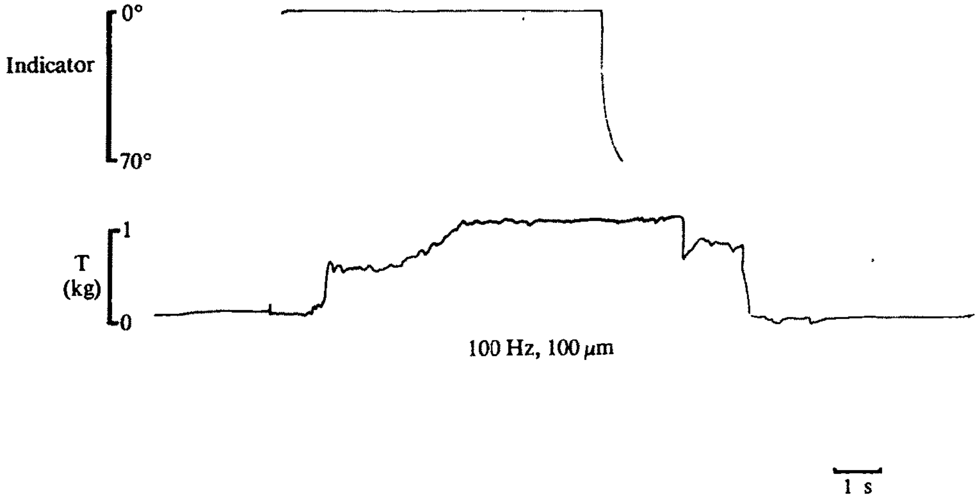

FIG. 4. This shows the effects of longitudinal vibration of *extensor hallucis longus* in D.I.McC. at 100 Hz, amplitude, for the period shown. The lower panel shows the tension record. note that the relaxed muscle was initially drawn out to its resting length and developed a passive tension of 0 4 kg. Vibration added an increment of tension due to involuntary reflex activity in the muscle—the 'tonic vibration reflex'. The upper trace is an indicator of the illusory rotation perceived for the interphalangeal joint of the big toe: the subject moved an indicator by hand at a velocity equivalent to that perceived velocity of toe movement (*see text*) He was not attempting to move the indicator as soon as the illusory movement was perceived. Instead, he delayed his indication until sure of the velocity of the illusory movement which he was attempting to duplicate.

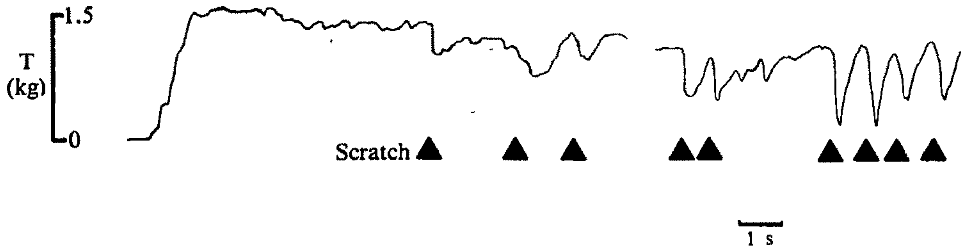

FIG. 5. This shows isometric tension developed through the transected tendon of *extensor hallucis longus* of D.I.McC. when he made an attempt to maintain a constant, active effort of dorsiflexion of his big toe. At the points marked, an experimenter scratched the skin of the plantar surface of the big toe with a blunt object: each scratch was a single firm movement distally.

tension fell during each stroke. This is illustrated in fig. 5. This response presumably corresponds to the flexor plantar response of normal subjects.

In similar experiments the subject again attempted constant efforts. This time, the distal phalanx of the toe was freed from its restraints, held gently in a side-to-side grasp by an experimenter, and then moved slowly into full plantar flexion, and back. Fig. 6 illustrates the results obtained. As the toe was moved into plantar flexion, contractile tension gradually fell, then rose again as the toe was moved back. This occurred despite the subject maintaining a constant voluntary effort.

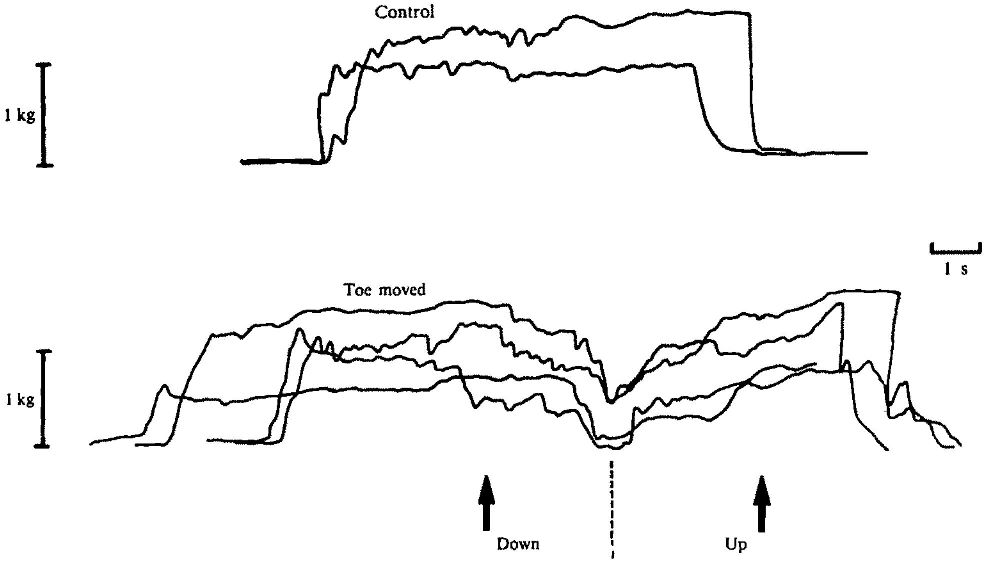

FIG. 6. This shows the isometric tension developed through the transected tendon of *extensor hallucis longus* of D.I.McC. when he made attempts to maintain constant, active efforts of dorsiflexion of his big toe. The upper panel shows control trials. The lower panel shows the effects of a slow movement into plantar flexion and back imposed by an experimenter on the interphalangeal joint of the big toe. Although the tendon was disconnected from the joint and the subject was attempting to maintain a constant effort, note that achieved tension fell as the toe was moved down and rose again as it was moved back.

DISCUSSION

The present study has shown that pulling or vibrating the exposed tendons of normal, awake subjects can give sensations of joint movement, even when the joints concerned are not moved. In all the cases reported, the sensations elicited were those of joint rotations in the direction which would normally stretch the muscles tested. The quantitative studies on one subject showed that detection levels were similar for movements imposed on the intact joint and for corresponding stretches imposed on a muscle through its exposed tendon (fig. 3). These findings, therefore, confirm and extend those of Matthews and Simmonds (1974). Moreover, they are in harmony with the findings that proprioceptive sensation is preserved after selective anaesthetization of joints and skin (Goodwin *et al.*, 1972; Gandevia and McCloskey, 1976; Clark *et al.*, 1979), and after total surgical removal of joints (Goodwin *et al.*, 1972; Moberg, 1972; Cross and McCloskey, 1973; Grigg *et al.*, 1973).

In all these experiments the muscle extensions applied were within the physiological range. In the disconnected tendon of *extensor hallucis longus* a tension of 0.4 kg was necessary to hold the muscle at its resting length, and an additional 0.1 kg was necessary to draw it out to the length corresponding to maximal plantar flexion. At these lengths, an additional active tension of 4 kg or more could be achieved by a maximal voluntary contraction. In the experiments on patients we estimate that similar tensions (up to 0.5 kg) were necessary to stretch the muscles as described.

The laboratory-based experiment reported here was carried out on one of the authors—a subject who had clear expectations of the qualitative results to be obtained. The disadvantages of the choice of such a subject are conceded but, given the nature of the procedure involved, recruitment of one or more physiologically naïve subjects was out of the question. The conclusions from the experiment depend, therefore, on the care and completeness of the controls—and these were given close attention throughout. In addition, it is quite unlikely that the subject's expectations could have determined the quantitative results obtained, so that the reproducibility of these results and their correspondence with the results obtained in tests on the intact toe (figs. 2 and 3) provide strong evidence against any influence of subjective bias.

The observations made in conscious patients at operation support and validate the findings on the volunteer subject. Considerable effort was used to avoid any possible influence of expectation of results in both the experimenter and the patients. The results here are in agreement with the earlier findings of Matthews and Simmonds (1974), but are apparently in conflict with those of Gelfan and Carter (1967) and Moberg (1972). As noted in the Introduction, Gelfan and Carter (1967) may well have concentrated only on sensations 'referable to the muscles', in which case their findings are not relevant to questions about proprioceptive sensations. Furthermore, their experiments seem to have been conducted sometimes under adverse conditions, as they were forced to discontinue some 'because of undue apprehension, complaints or pain, or . . . language problems'. Moberg's 1972 report is unequivocal, but it is very brief, and apart from indicating that attention was given to proprioceptive sensations, gives insufficient detail to judge whether its methods differed significantly from those used here.

The accompanying paper by Moberg (1983), however, now confirms that proprioceptive sensations can be elicited by tendon pulling, and joins Matthews and Simmonds (1974) and the present study in failing to confirm the negative results of Gelfan and Carter (1967).

It is important to distinguish a conflict over facts from one over interpretation. There is no doubt that some patients in Moberg's (1983) series reported definite proprioceptive sensations. To this extent, there is no disagreement over the facts. However, we take such findings to indicate a kinaesthetic role for intramuscular receptors, whereas Moberg favours a role for receptors in the skin overlying the muscles, and has stressed this interpretation throughout his paper. Moberg does not specify the experimental conditions which made the crucial difference for the report of sensations in his patients, except in terms of this interpretation. Each time there were proprioceptive sensations, he notes that there was visible deformation of the skin in the forearm and implies a causal relationship between the two. Whether other factors may have contributed is not considered. In this connection, he does not comment on the report by Gelfan and Carter (1967) that some of their patients reported 'pulling and movements of the skin overlying the stretched muscles', and his own Case 4 reporting a 'pumping' in the arm, without the report of associated proprioceptive sensations. Our patients were unanimous in reporting the kinaesthetic sensations, and we are therefore less well placed than Moberg to discover why some of his patients failed to report them. We note, however, that he pulled the flexor tendons of relaxed muscles while the digits were flexed (and, possibly in some cases, the wrist also), so that there may have been a considerable amount of 'slack' to be taken up in the tendons. In addition, his pulls stopped when 'the "stop" was reached'. It is difficult to be sure that significant muscle stretch occurred under these circumstances. Our patients were studied with their digits extended, so that there was no 'slack' in the tendons, and we have estimated the forces applied in pulling the tendons the distances specified. (In the test postures used here the muscles were not at the limit of their physiological lengths, as the wrists were held straight. Extension of the wrist through approximately a further 60 deg is possible from this posture, and our measurements and anatomical calculations show that this can extend the digital flexors a further 10 to 15 mm.)

The most likely interpretation for the findings we report is that intramuscular receptors were responsible. This would fit with the wealth of other evidence in favour of this view (for reviews *see* Goodwin *et al.*, 1972; Goodwin, 1976; Matthews, 1977; McCloskey, 1978; Burgess *et al.*, 1982). In the present experiments, we did not attempt specifically to exclude the possibility that remote, nonmuscular receptors were involved. In the laboratory experiment on the transected tendon of D.I.McC., stretch of less than a millimetre was reliably detected as specific joint movement: at the conclusion of data collection, when the subject was permitted to sit forward and look directly at the tendon in his foot while such displacements were imposed, he could not *see* the movement of the tendon and its connections which elicited the sensations. Neither the subject nor the experimenters noted any dimpling of the skin over the muscle belly in the leg. It seems almost inconceivable that such small stretches could have produced their very specific sensory effects by exciting remote cutaneous or fascial receptors.

Moberg (1983) is concerned that proprioceptive sensations may be said to be referred to a single joint as a result of activating receptors within a muscle which crosses two or more joints. This is, of course, a large but unresolved difficulty for his own hypothesis which has it that receptors in remote skin and fascia underlie such sensations. However, where a muscle crosses several joints, the potential ambiguity of signals of muscle stretch could be resolved if the nervous system were to refer to simultaneously received signals from other muscles which cross only some of those joints. This matter has been considered elsewhere (for example, Goodwin *et al.*, 1972). Thus, in the specific case of sensations referred to the interphalangeal joint of the big toe when *extensor hallucis longus* is stretched, the absence of a simultaneous change in length in other muscles which cross the metatarsophalangeal joint or the ankle joint, but not the interphalangeal joint, can be held responsible for the referral being made to the correct joint.

The stretch-sensitive muscle receptors most likely to underlie the sensations reported here are the muscle spindles. Longitudinal vibration of the tendon evoked illusory movements, an observation supporting the arguments of Goodwin *et al.* (1972) based on their description of similar illusions induced by transverse vibration of a tendon through the skin. Transverse vibration of relatively large amplitudes ($\sim$0.5 mm) is necessary to induce the illusions, and has been demonstrated in man to excite spindle secondary endings and Golgi tendon organs as well as spindle primary endings (Burke *et al.*, 1976). Longitudinal vibration of smaller amplitudes, such as those used here, is a more specific stimulus for the spindle primaries (Brown *et al.*, 1967; Matthews, 1972). The local spread of vibration into the foot of the subject in this experiment unfortunately limited the systematic study of the vibratory illusions here. At the frequencies of vibration employed there is likely to have been significant activation of Pacinian corpuscles in the foot, and such activation has been shown to raise the thresholds for detection of various cutaneous stimuli (Ferrington *et al.*, 1977). If a similar masking of proprioceptive inputs is caused by activation of Pacinian receptors, the difficulties experienced here may well be explained.

In the exposed tendon of the volunteer subject two additional experiments were carried out, and these were illustrated in figs. 5 and 6. The first of these demonstrated a fall in the tension achieved through *extensor hallucis longus* during firm stroking or scratching of the plantar surface of the big toe: as noted in the Results, this is presumably a component of the normal flexor plantar response. The second experiment demonstrated a fall in tension as the terminal joint of the toe was rotated into plantar flexion, with a return to control levels as the toe was rotated back to its control position. These changes in active tension occurred with the rotated joint disconnected from the tendon and despite the subject's attempts to maintain a constant voluntary effort. Although the joint movement was imposed through a gentle grip of the sides of the toe, it is possible that distortion of the skin on the plantar surface of the toe was sufficient to activate cutaneous receptors and elicit another manifestation of the plantar response. Alternatively, the response may indicate that sensory receptors in the skin, joint, or in the antagonist muscle may have the physiological role of inhibiting active contraction in a muscle where a joint rotates in such a way as to lengthen that muscle. This could allow the muscle to lengthen with the joint rotation without increasing the tension it applies at the joint. Such a response would be similar to that described by Blaschke *et al.* (1952), who studied below-elbow amputees and found that the voluntary tension achieved by the elbow flexors, when disconnected from the joint, was reduced as the elbow joint was passively extended. In experiments on the knee joint of the cat, Cohen and Cohen (1956) made essentially similar observations, but a recent report by Baxendale and Ferrell (1981) is in direct conflict with this. The matter deserves further study in man should the opportunity arise for such experimentation.

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AN EXPERIMENTAL STUDY OF PERIPHERAL NERVE REGENERATION AFTER X-IRRADIATION

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SUMMARY

The effects of x-irradiation on peripheral nerve regeneration in the mouse were examined using quantitative and ultrastructural techniques. One hind limb was exposed to 15 or 20 Gy one day before, or 20 Gy three days after the right sciatic nerve was crushed. The distal sciatic and posterior tibial nerves were examined up to 120 days after injury. Irradiation before injury initially reduced the proliferation of endoneurial cells although cell numbers reached control levels after a few weeks. Myelination was delayed but not prevented, and after exposure to 20 Gy the myelin sheaths remained abnormally thin. In nerves irradiated after injury endoneurial cellular proliferation was severely and persistently reduced, and many fibres showed segmental absence of myelin. Internodes abutting the nonmyelinated segments were abnormally long, suggesting that contact with adjacent internodes may limit elongation of internodes during normal regeneration.

INTRODUCTION

Schwann cell proliferation is thought to play an important part in recovery of function after peripheral nerves are cut or crushed. From the third day after injury Schwann cells in the distal nerve segment proliferate for three to four weeks (Abercrombie and Johnson, 1946; Bradley and Asbury, 1970). Axonal and myelin debris is partially degraded by the dividing cells before being transferred to endoneurial macrophages (Thomas, 1964; Williams and Hall, 1971). Proliferation eventually gives rise to the cells which myelinate the regenerated axons, although more Schwann cells are present when division ceases than are needed to form internodes (Jacobs and Cavanagh, 1969).

Low dosage x-irradiation impairs proliferation of mammalian cells (Puck and Marcus, 1956; Puck, 1959). Irradiation of peripheral nerve has been shown to suppress the cellular response to crush injury (Cavanagh, 1968*a*, *b*; Edds, 1955), but little is known as to its effects on degradation of debris, axonal regeneration and myelination (Edds, 1955). This paper describes quantitative and ultrastructural studies on irradiated peripheral nerve, up to 120 days after a crush injury.

The effects of irradiation on mammalian cells depend on the mitotic activity at the time of exposure (Fabrikant, 1969; Little, 1969). In adult peripheral nerve Schwann cells are amitotic unless stimulated to divide by nerve injury (Bradley and Asbury, 1970). It was considered of interest to determine whether proliferating Schwann cells are more radiosensitive than those of intact peripheral nerve. In the present study nerves irradiated three days after a crush injury were compared with those irradiated one day before injury.

The results show that irradiation before nerve injury delays the formation of myelin sheaths, which remain abnormally thin. In nerves irradiated after injury myelin is not only thin but also discontinuous. These results are correlated with changes, following irradiation, in the pattern of Schwann cell proliferation.

METHODS

Adult male CFLP mice were used. All experimental procedures were performed on the right hindlimb only, and were done under pentobarbitone anaesthesia (0.06 mg/g body weight, administered intraperitoneally). Animals were divided into 4 groups, each of 14 mice. In control mice (group I) the sciatic nerve was crushed at midthigh level using fine watchmakers' forceps applied firmly for 20 s. In groups II and III the hindlimb was irradiated one day before the sciatic nerve was crushed. These groups received 15 and 20 Gy (1500 and 2000 rads), respectively. In group IV the limb was exposed to 20 Gy three days after crushing the sciatic nerve. Irradiation was carried out on a Pantak x-ray machine at 240 kVp and 15 mA with filtration of 0.25 mm Cu and 1 mm Al, and a half value layer of 1.12 mm Cu. The focal skin distance was 400 mm giving a dose rate of 1.52 Gy/min. The rest of the animal was shielded with 6 mm lead. Neurological recovery was assessed daily by observing the animal's ability to walk across a wire grid with the bars 2 cm apart, and the response when the mouse was lifted by the tail (normally accompanied by extension and fanning of toes) or when the foot was firmly pinched. Mice were killed at 2 day intervals for 2 weeks after the nerve crush and at less frequent intervals thereafter up to 120 days.

Under pentobarbitone anaesthesia, mice were perfused through the left ventricle with 3 per cent glutaraldehyde-1 per cent paraformaldehyde in 0.07 M Na cacodylate buffer (pH 7.2 to 7.4). The sciatic nerve, soleus and extensor digitorum longus muscles were removed, postfixed in 1 per cent osmium tetroxide, dehydrated in graded alcohols and embedded in Araldite. In some animals the posterior tibial nerve was removed, processed as above, and single fibres were teased in unpolymerized Araldite on glass slides. Blocks were taken from the sciatic nerve, 4 to 5 mm distal to the crush, and through the endplate regions of soleus and extensor digitorum longus. Sections at 1 μm were stained with toluidine blue and ultrathin sections with uranyl acetate and lead citrate.

Quantitative Methods

Transverse 1 μm sections of the sciatic nerve were examined under a 100 × oil-immersion objective. In each nerve at least 500 axons > 2 μm in maximum diameter (measured with an eyepiece graticule) were counted and the proportion without myelin sheaths was determined. These were designated 'nonmyelinated' fibres to distinguish them from smaller unmyelinated fibres. The sections were examined in random order without knowledge of the experimental group. In some sciatic nerves the proportion of axons > 2 μm in diameter which were myelinated was also determined from electron micrographs. The electron micrographs were enlarged to × 5000 (calibrated by means of a grating replica, 2160 lines/mm) and the maximum diameters measured with a ruler. The light microscopic data correlated closely with those obtained from electron micrographs (coefficient of correlation = 0.993).

Transverse 1 μm sections of the tibial nerve were examined under a 40 × oil-immersion objective and counts were made of all nuclei excluding perineurial, endothelial and mast cell nuclei. The average was calculated from counts at three levels, 10 to 15 μm apart. Longitudinal 1 μm sections were then cut from the same nerves and the mean length of 100 nuclei was obtained from measurements with an eyepiece graticule. Nuclear counts in transverse sections were corrected for changes in nuclear length (Abercrombie and Johnson, 1946).

Axonal diameter and myelin sheath thickness were measured on light photomicrographs which were enlarged × 3500. Representative fields were photographed and the axonal and myelin sheath areas of at least 500 fibres in each nerve were measured by tracing their outlines with a cursor on a MOP AM-03 image analyser (Kontron). The MOP was linked to a Research Machines 380Z computer programmed to calculate the axonal and total fibre diameters assuming axonal circularity (*see* Karnes *et al.*, 1977). Axons were grouped, according to diameter, at intervals of 0.5 μm, and the mean myelin sheath thickness and standard deviation were calculated for each group.

At least 50 teased single fibres in each nerve were examined under 10 × and 40 × objectives. The internodal length was measured by means of an eyepiece graticule and the mean external diameter of each internode was calculated from three or more measurements at points away from the nucleus. Preliminary observations in group IV suggested that some regenerated internodes, abutting nonmyelinated segments of axon, were abnormally long. A t-test was used to compare their length with other internodes in the same nerves. Since the standard deviation varied in different nerves but the ratio of standard deviation to mean remained approximately constant, the data were transformed logarithmically for statistical analysis (Bishop, 1971). To try to determine whether there was asymmetrical elongation of internodes abutting nonmyelinated segments, the position of the Schwann cell nucleus was recorded, where visible. The distance from the midpoint of the nucleus to the adjacent myelinated internode was measured and expressed as a percentage of the overall internodal length. The position of the Schwann cell nucleus was also determined in other internodes in group IV, and in the control group I.

RESULTS

Clinical Observations

Following nerve crush all mice showed flaccid paralysis and did not react when the foot was pinched. By 14 days all animals responded to pain, and in group I could, in addition, grip the bars of a wire grid and extend and fan the toes. In group II return of motor function was delayed by 3 or 4 days. Mice in groups III and IV showed little motor recovery during the first month and slow improvement thereafter. Irradiation caused hair loss which became apparent 3 to 5 days after 20 Gy and 2 weeks after 15 Gy. Exposure to 20 Gy resulted in skin erythema and swelling of the foot which subsided after the first month. The wounds healed without complication.

Light Microscopy

The onset of myelination was delayed following irradiation. In group I (controls) myelinated fibres were first seen at 8 days but only at 12 days in group II and 18 days in group III (fig. 1). In group IV a few myelinated fibres were present from 12 days but they remained in small proportion up to 18 days.

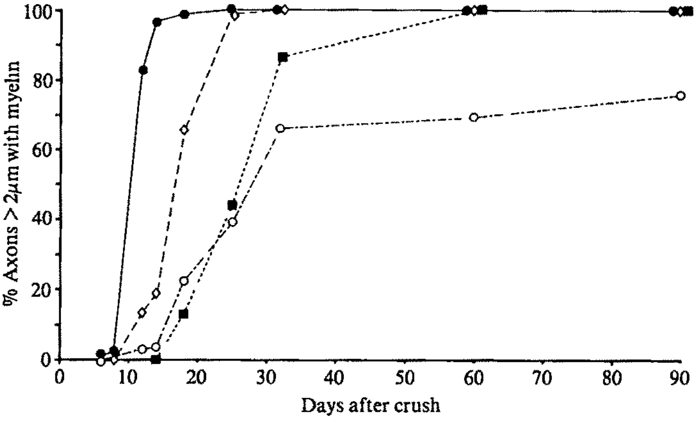

FIG. 1. Percentage of large axons (> 2 μm in diameter) in the sciatic nerve which were surrounded by myelin, with increasing survival time after injury. Each point represents one animal. Group I (●——●), group II (◇---◇), group III (■···■), group IV (○----○).

In group I, all axons greater than 2 μm in diameter were myelinated within 1 week after myelination was first seen, indicating synchrony of myelination across the whole nerve. In contrast, myelination was not well-synchronized in irradiated nerves. Not only was there a delay in the onset of myelination but the delay varied considerably for fibres within the same nerve. This lack of synchrony was most marked in group IV in which, although some axons were myelinated as early as 12 days, the proportion of myelinated axons continued to rise until 32 days. The thickness of the myelin sheaths in individual nerves varied widely after irradiation, particularly in group IV (fig. 2). Axons with a relatively thick myelin sheath were interspersed with nonmyelinated or very thinly myelinated fibres. After 60 days, in groups I, II and III all axons greater than 2 μm in diameter showed some degree of myelination but in group IV many large axons lacked myelin (fig. 3). In longitudinal sections of nerves in group IV, myelinated internodes were seen to abut nonmyelinated lengths of axon. The relationship between myelinated and nonmyelinated segments was defined more clearly in teased fibre preparations.

The number of nuclei in unirradiated nerves increased rapidly after injury, reaching peak levels of about 7 times normal between 2 and 4 weeks (Table 1). Thereafter the number decreased to about 3.5 times that before injury. The initial increment was diminished by prior irradiation (groups II and III) but nuclear counts reached control levels by 18 days in group II and by 46 days in group III. Nerves in group IV, irradiated after injury, contained, at all times, fewer nuclei than the other groups.

The relation between axon diameter and myelin sheath thickness was determined at 32, 60 and 90 days (fig. 4). At 32 days fibres in group II were hypomyelinated compared with controls but by 60 days myelin thickness was similar to control values. In groups III and IV a substantial proportion of axons was nonmyelinated at

[*text continued on p. 46.*]

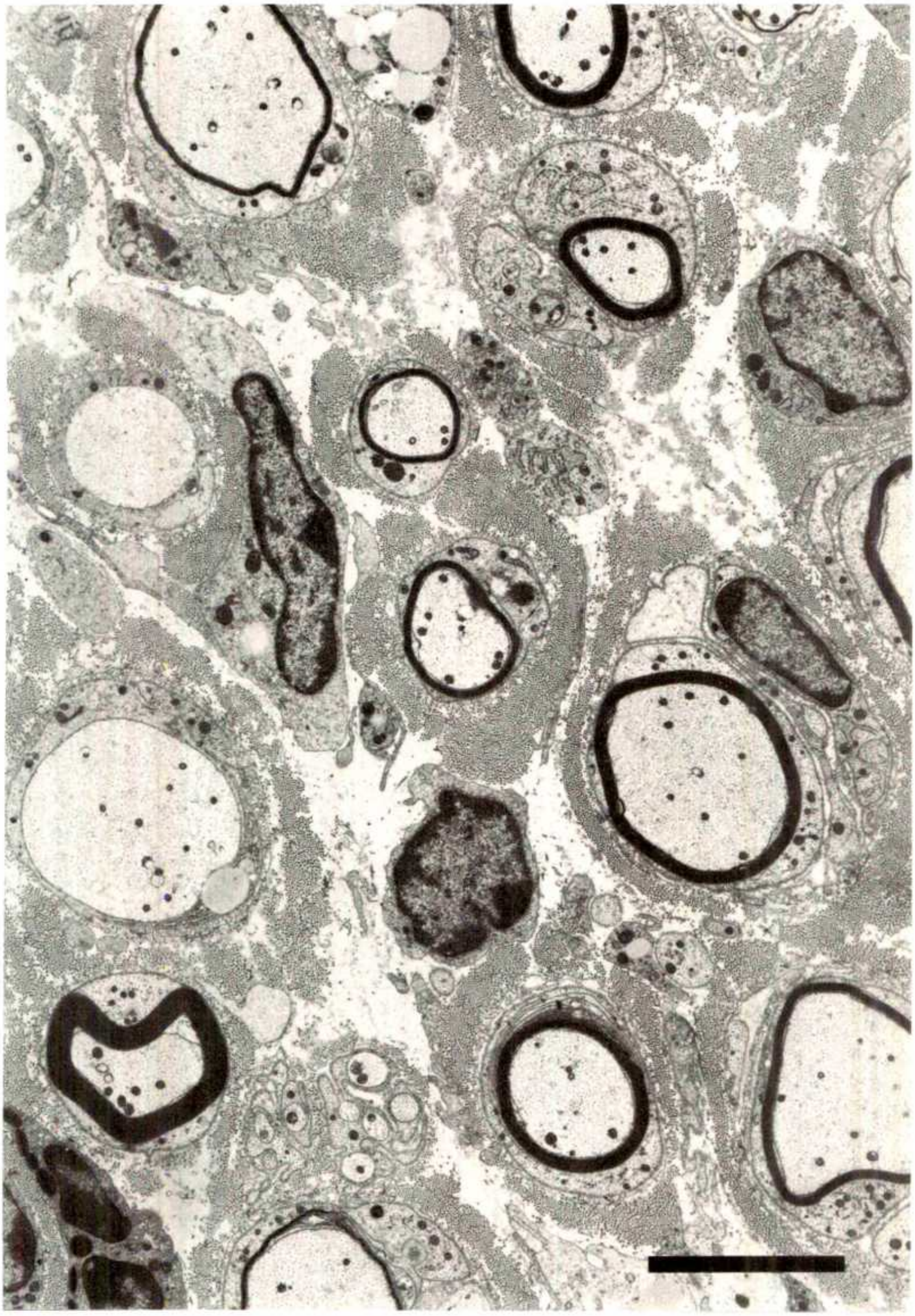

FIG. 2. Electron micrograph of sciatic nerve from group IV, 32 days after injury. In this transverse section, 4 to 5 mm distal to the crush, some axons are well myelinated whilst others are thinly or nonmyelinated. Bar = 5 μm.

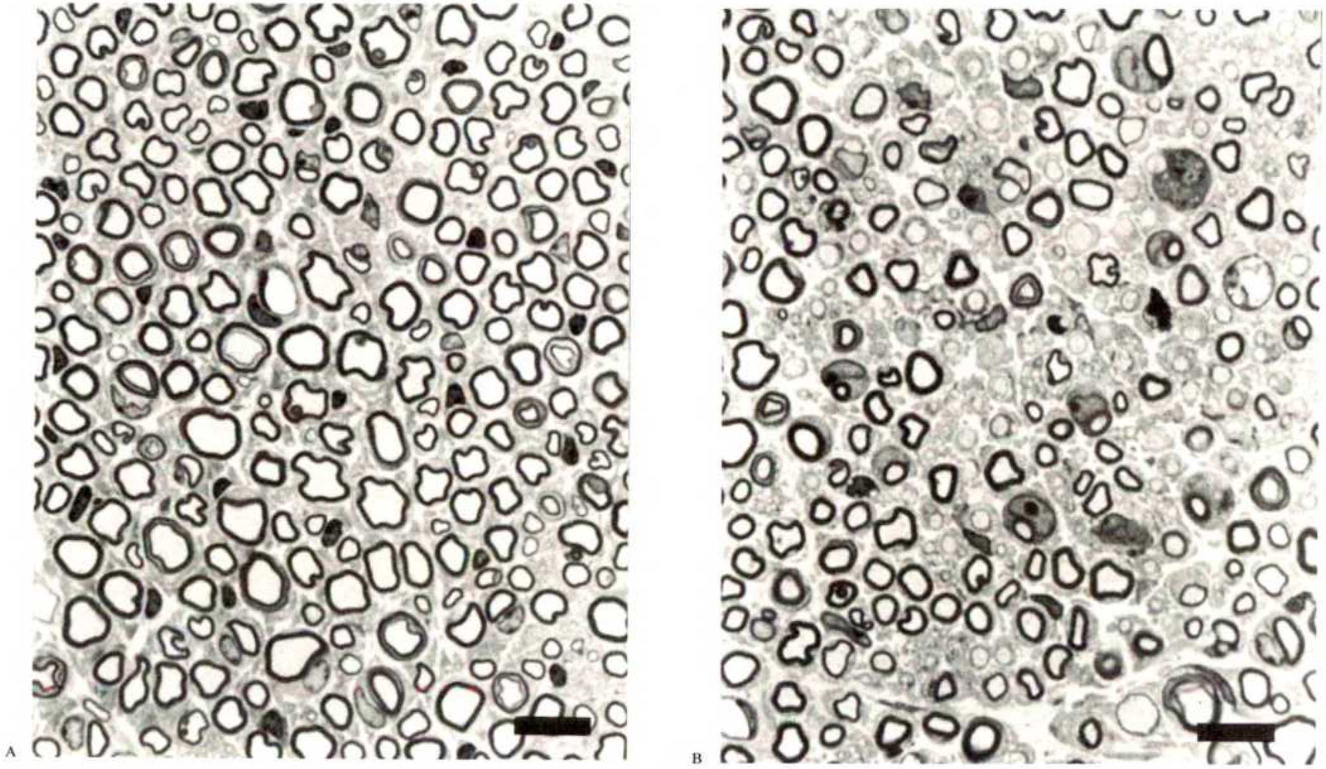

FIG. 3. Transverse sections of sciatic nerves from groups I (A) and IV (B), 4 to 5 mm distal to crush, after 90 days. In group I all large axons are well myelinated, while in group IV many still lack myelin sheaths. Bar = 10 μm.

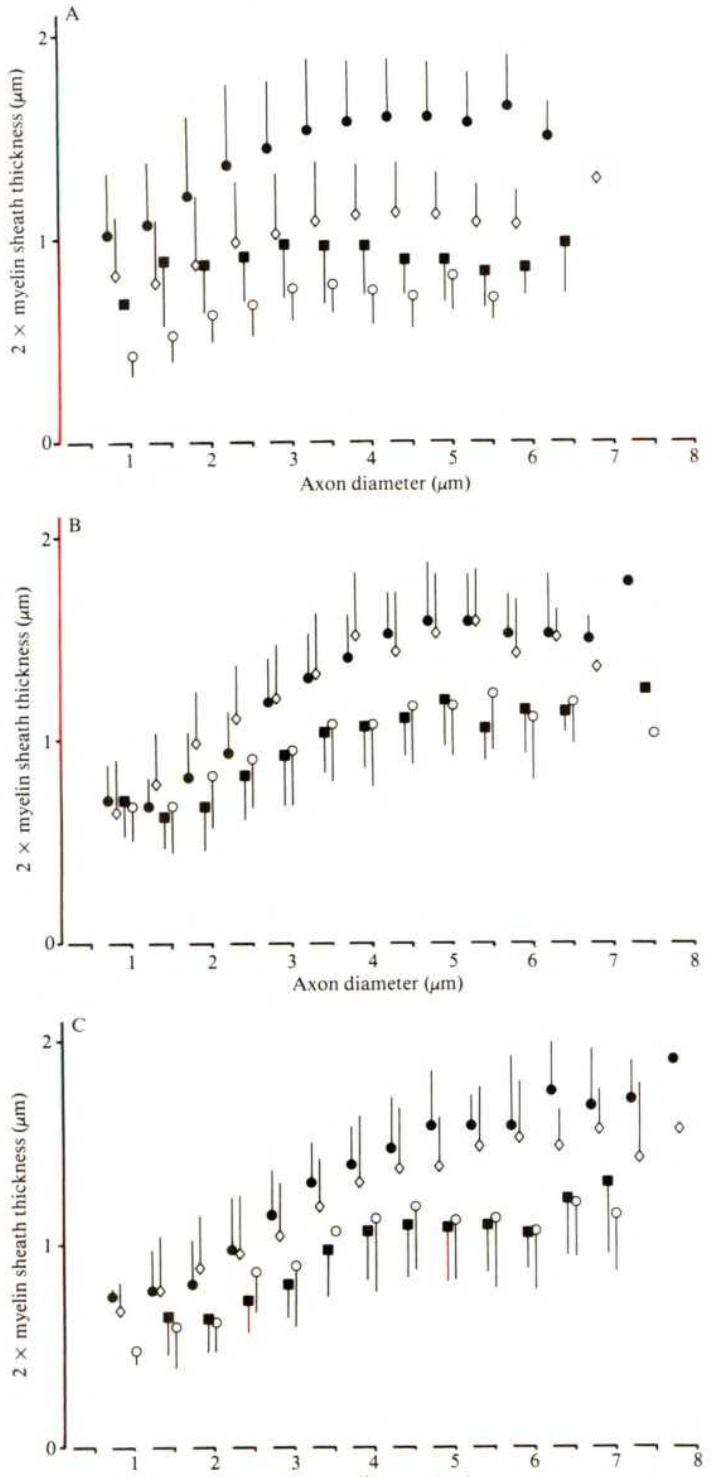

FIG. 4. Relationship between 2× myelin sheath thickness and axon diameter in the sciatic nerve at 32 (A), 60 (B) and 90 (C) days. Vertical bars indicate one standard deviation from the mean. One animal in each group was examined at each time and at least 500 fibres were measured. Group I (●), group II (◊), group III (■), group IV (○).

TABLE 1. NUCLEAR COUNTS IN TIBIAL NERVE

Survival (days)	*Group I*	*Group II*	*Group III*	*Group IV*
0	126*	—	—	—
2	139	—	—	—
4	227	194	151	163
6	505	287	—	205
8	471	—	—	—
12	839	491	—	270
14	849	620	435	286
18	790	691	413	423
25	686	700	414	446
32	749	591	551	298
46	440	479	475	—
60	398	373	434	340
90	427	348	296	205

Group I, nerve crush only. Group II, 15 Gy 1 day before crush. Group III, 20 Gy 1 day before crush. Group IV, 20 Gy 3 days after crush. * Total number of nuclei excluding perineurial, endothelial and mast cell nuclei, and corrected for changes in nuclear length (Abercrombie and Johnson, 1946).

32 days but where present the myelin sheath was very thin. Fibres in groups III and IV, particularly those of larger diameter, remained relatively thinly myelinated at 60 and 90 days compared with groups I and II. The distribution of axonal diameters of myelinated fibres at 32 and 90 days is shown in fig. 5. The mean diameters increased slightly in all groups over this period. No obvious differences were apparent between groups.

Teased single fibres were examined in all experimental groups at 90 days and, in addition, at 60 and 120 days in groups I and IV. The internodal lengths and corresponding external diameters of at least 50 fibres were measured in each nerve. No relation was found in any group between regenerated internodal length and fibre diameter. The mean internodal length was slightly greater in irradiated nerves than controls although individual values varied widely (Table 2). Along many nerve

TABLE 2. MEAN LENGTH OF REGENERATED INTERNODES IN POSTERIOR TIBIAL NERVES

Survival (days)	*Experimental group*		*Mean internodal length (μm) ± SD*
60	I	(242)*	290 ± 71
60	IV	(199)	372 ± 101
90	I	(318)	296 ± 63
90	II	(269)	308 ± 90
90	III	(194)	318 ± 80
90	IV	(145)	462 ± 214
120	I	(231)	273 ± 63
120	IV	(170)	315 ± 137

* Number of internodes.

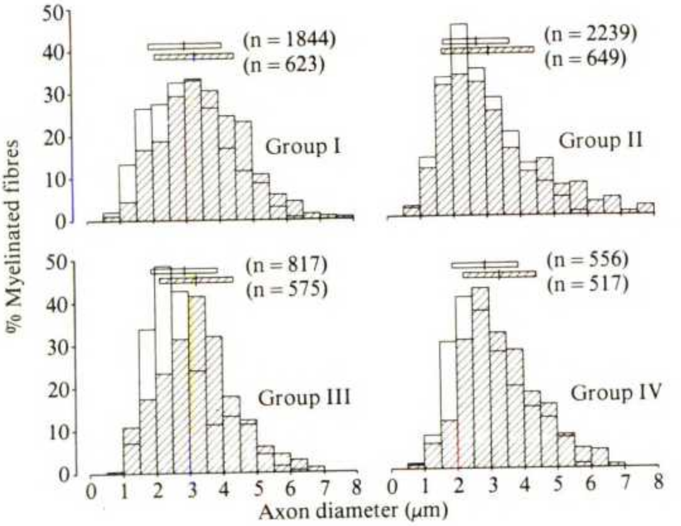

FIG. 5. Axon diameter histograms of myelinated fibres in the sciatic nerve at 32 days (nonhatched) and 90 days (hatched). Horizontal bars indicate one standard deviation from the mean.

fibres in group IV, nonmyelinated lengths of axon interrupted sequences of myelinated internodes. Nonmyelinated segments ranged in length from approximately 15 μm to more than 200 μm. The longer nonmyelinated segments were difficult to tease so that a representative set of measurements could not be obtained. The lengths of internodes which abutted nonmyelinated segments, compared with other internodes in the same nerves, are shown in Table 3. The former were significantly longer than the latter ($P < 0.001$), and their Schwann cell nuclei tended to lie closer to the adjacent myelinated internode than to the nonmyelinated segment (Table 4). However, there was considerable variation in the nuclear position in the irradiated nerves as well as in controls.

TABLE 3. ANALYSIS OF REGENERATED INTERNODAL LENGTH IN GROUP IV IRRADIATED NERVES ACCORDING TO RELATION OF INTERNODES TO NONMYELINATED SEGMENTS

Survival (days)	*Relation to nonmyelinated segments*		*Mean internodal length (μm) ± SD*
60	Abutting	(66)*	431 ± 106**
60	Not abutting	(133)	342 ± 83
90	Abutting	(67)	629 ± 175**
90	Not abutting	(78)	320 ± 120
120	Abutting	(44)	446 ± 173**
120	Not abutting	(125)	270 ± 82

* Number of internodes. ** $P < 0.001$.

TABLE 4. POSITION OF SCHWANN CELL NUCLEI* IN CONTROL MICE, AND IN GROUP IV IRRADIATED MICE WITH DISCONTINUOUSLY MYELINATED FIBRES

Survival (days)	*Experimental group*		*Relation to nonmyelinated segments*	*Nuclear position (%) ± SD*
60	I	(99)**	—	50.2 ± 25.1
60	IV	(51)	Abutting	46.1 ± 17.7
60	IV	(105)	Not abutting	51.7 ± 21.8
90	I	(88)	—	50.4 ± 22.7
90	IV	(37)	Abutting	45.6 ± 11.3
90	IV	(65)	Not abutting	51.3 ± 19.6
120	I	(106)	—	50.7 ± 25.5
120	IV	(28)	Abutting	41.7 ± 17.5
120	IV	(101)	Not abutting	49.6 ± 20.7

* Measured to adjacent internode and expressed as a percentage of overall internodal length. ** Number of internodes.

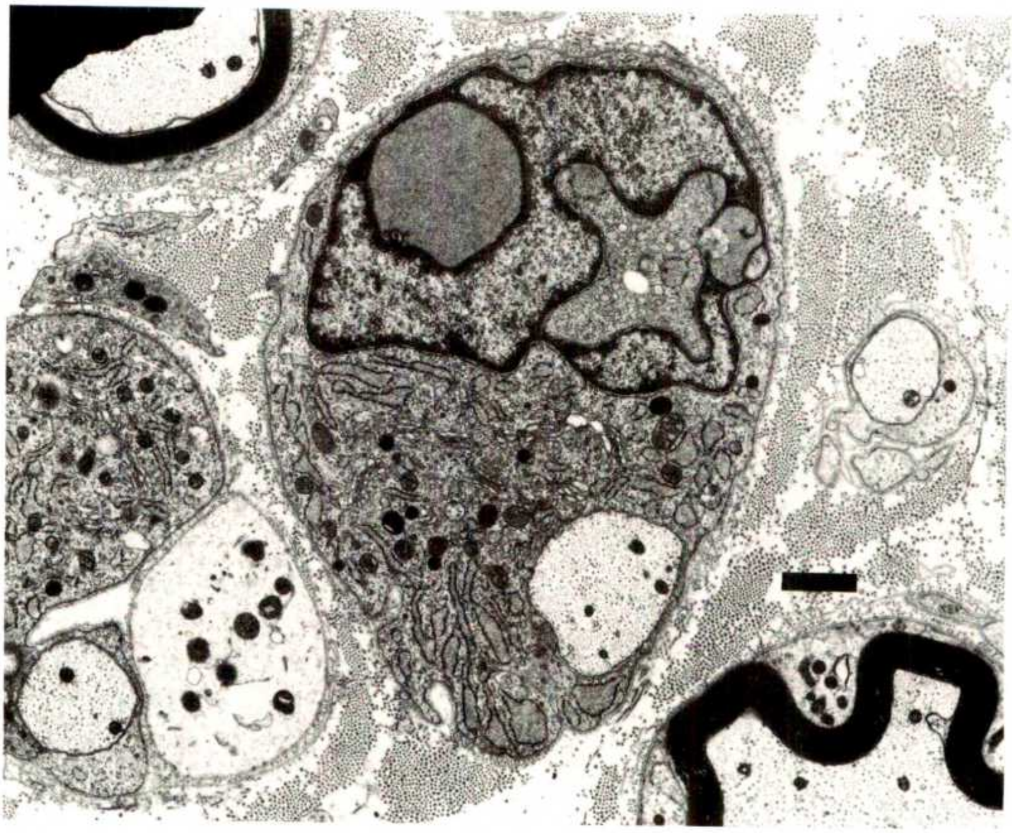

FIG. 6. Electron micrograph of sciatic nerve from group IV, 60 days after injury, showing a highly convoluted nucleus in a Schwann cell which is associated with a nonmyelinated axon. Bar = 1 μm.

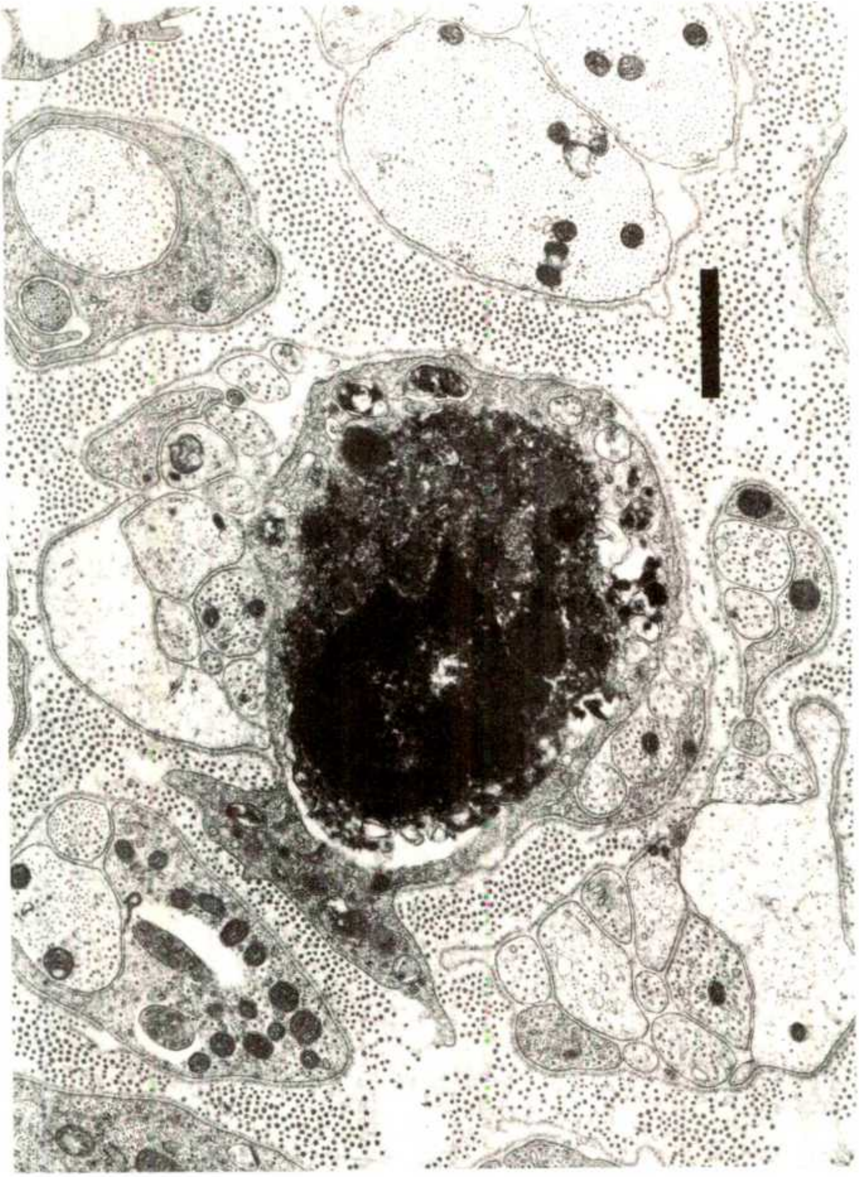

FIG. 7. Electron micrograph of sciatic nerve from group II, 14 days after injury, showing degenerating Schwann cell. The pyknotic Schwann cell nucleus is surrounded by granular cytoplasm which contains clumps of electron dense material. Bar = 1 μm.

Electron Microscopy

Myelin degradation proceeded normally in irradiated nerves (*see* Williams and Hall, 1971). Large numbers of endoneurial macrophages were present from the 4th day. Following the appearance of macrophages there was progressive disappearance of complex membranous profiles from the Schwann cell cytoplasm and after 2 weeks few Schwann cells in any group contained myelin debris. The time course of disappearance of macrophages was similar in all experimental groups and was in agreement with the findings of Williams and Hall (1971). A small number of debris-laden macrophages persisted around blood vessels and adjacent to the perineurium for many weeks after injury.

Abnormalities were numerous in Schwann cells from the first week after irradiation and included micronuclei, large convoluted nuclei (fig. 6) and the presence of multiple nuclear profiles within the same cell. Few mitotic figures were seen but these were not obviously abnormal. Occasional cells contained pyknotic nuclei undergoing disintegration (fig. 7). The cytoplasm of some Schwann cells was dense and granular (fig. 8) whereas other cells had distended, lucent cytoplasm

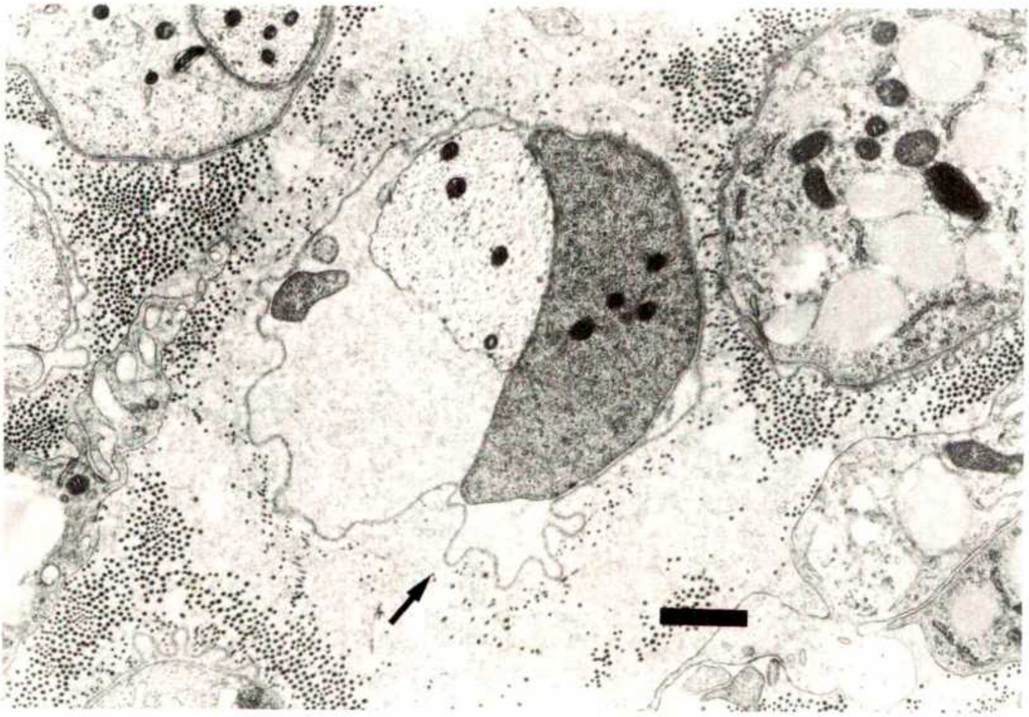

FIG. 8. Transverse section of sciatic nerve from group III, 14 days after injury. This electron micrograph shows an axon which is incompletely ensheathed by Schwann cell processes with dense granular cytoplasm. Redundant basal lamina is thrown into folds (arrow). Bar = 1 μm.

depleted of organelles. Endothelial and perineurial cells appeared normal but a persistent increase in endoneurial space in all irradiated nerves suggested oedema.

Regenerating axons extended at least 4 to 5 mm distal to the crush at 4 days, and into the endplate regions of soleus and extensor digitorum longus at 8 days, in all experimental groups. A small number of axons in both control and irradiated nerves contained clusters of complex membranous profiles or dilated cisternae. Despite the delay in myelination caused by irradiation, the ultrastructural appearance of the myelin, where present, was normal. Segmental absence of myelin was a frequent finding in group IV up to 120 days after injury. The nonmyelinated segments of axon were usually incompletely covered by Schwann cell cytoplasm. Some axons were surrounded by redundant, convoluted basal lamina with only a few, slender, interposing Schwann cell processes (fig. 8), while occasional axons lacked any Schwann cell investment at all for considerable lengths (fig. 9). Well-formed heminodes were present at the junctions between myelinated and nonmyelinated segments of axon (fig. 10). In a few fibres the myelin sheaths tapered towards the nonmyelinated segments as lamellae terminated in successive series of myelin loops along the axolemma (fig. 11).

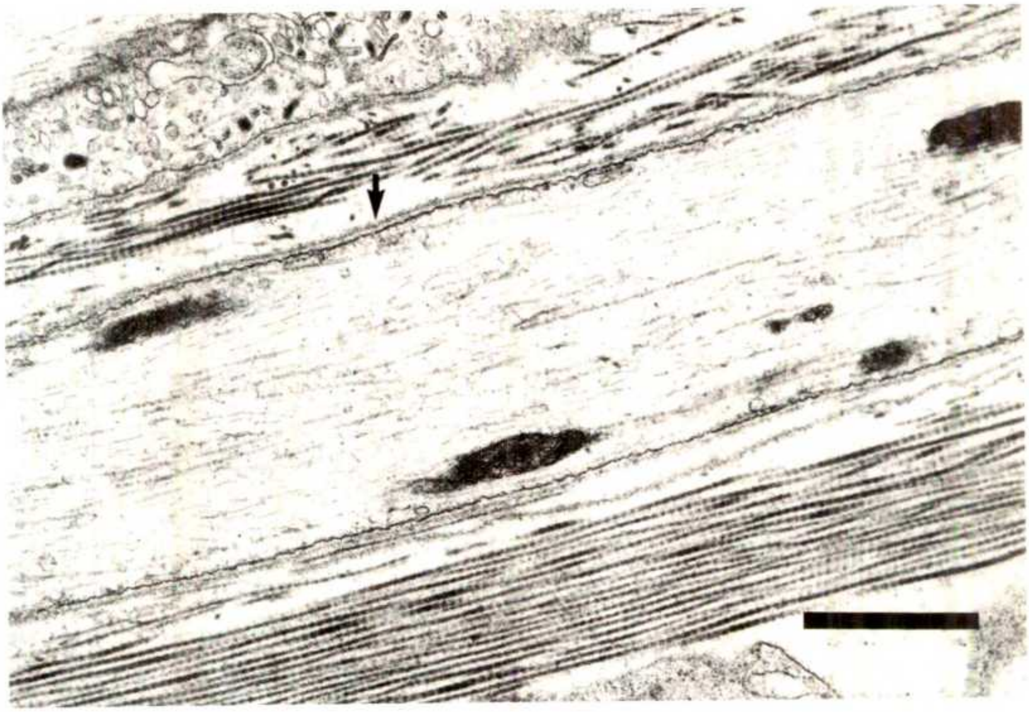

FIG. 9. Electron micrograph of sciatic nerve in group IV, 32 days after injury, sectioned longitudinally. The axolemma of a nonmyelinated fibre is apposed to basal lamina (arrow) without intervening Schwann cell processes. Bar = 1 μm.

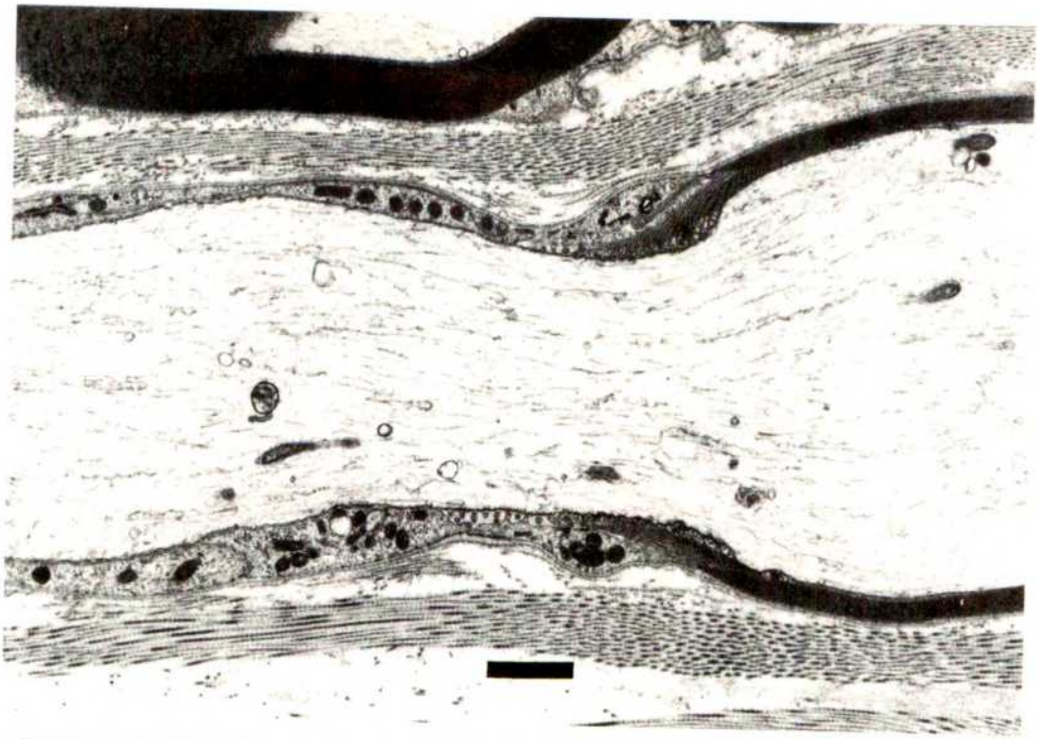

FIG. 10. Longitudinal section of sciatic nerve in group IV, 120 days after injury. This electron micrograph shows a well-formed heminode at the junction between a myelinated internode and a nonmyelinated segment of axon. Bar = 1 μm.

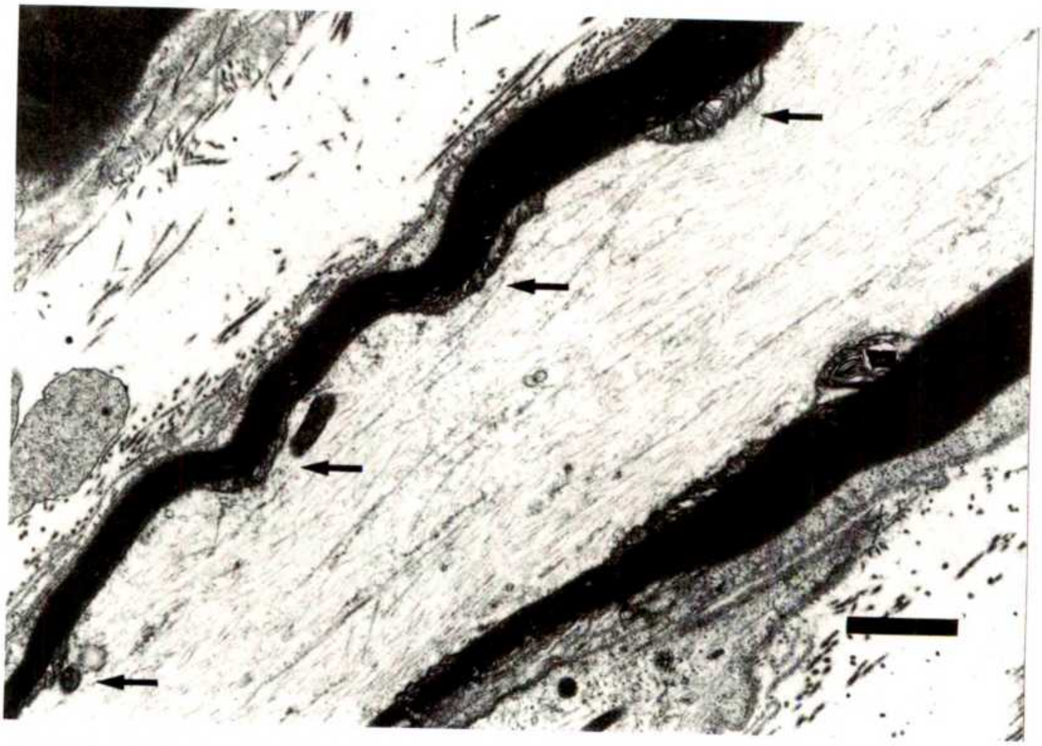

FIG. 11. Longitudinal section of sciatic nerve in group IV, 120 days after injury. In this electron micrograph the myelin sheath tapers towards a heminode (not shown) as lamellae terminate in successive series of myelin loops (arrows). Bar = 1 μm.

DISCUSSION

The normal response of peripheral nerve to a crush injury includes a marked increase of Schwann cells in the distal nerve segment (Abercrombie and Johnson, 1946). X-irradiation is known to suppress this proliferative response (Cavanagh, 1968*a*, *b*). Results of the present study indicate that irradiation has, in addition, marked effects on myelination, which can be correlated with the reduced proliferation of Schwann cells.

Irradiation, in doses comparable to those used in the present study, delays mitosis and limits cell division (*see* Little, 1968). Irradiation of nerves before crush injury suppressed endoneurial cellular proliferation for a few weeks but cell numbers then returned to control values. Although myelination was delayed it was not prevented, possibly reflecting the late recovery in the number of Schwann cells. Of relevance is the work of Hall and Gregson (1977) who found that inhibition of Schwann cell mitosis with mitomycin C delayed myelination of regenerated axons for at least 30 days. Schwann cells may have to undergo a certain number of divisions before myelination can occur.

Edds (1955) reported that irradiation caused 'clogging' of neurilemmal tubes with debris, and that this impeded axonal regeneration. His conclusion was based on counts of myelinated fibres and did not take into account the delayed onset of myelination. The evidence from the present study is that motor axons, at least, regenerate normally despite irradiation. However, impaired regeneration of some fibres cannot be excluded.

Schwann cell proliferation was more severely reduced by irradiation 3 days after crushing than 1 day before injury. Similar findings were reported by Edds (1955). The present work shows that the reduction persists for at least 90 days and that the number of myelinating cells is insufficient for continuous myelination, leading to segmental absence of myelin along many axons. The delay in clinical recovery may reflect continued conduction block at transitions between myelinated and nonmyelinated parts of the axon (*see* Waxman and Foster, 1980). The mean internodal length was not significantly increased in fibres irradiated before injury. However, in the discontinuously myelinated fibres which resulted from irradiation after injury, internodes abutting nonmyelinated segments were significantly longer than other internodes in the same nerves. The differential elongation of internodes suggests that contact between adjacent internodes may play a part in determining internodal length after nerve injury.

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THE ENZYME HISTOCHEMISTRY OF THE CHOROID PLEXUS

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SUMMARY

Although there is some evidence that extrachoroidal sites for the production of cerebrospinal fluid (CSF) are important, the choroid plexuses in the ventricles contribute the major part of CSF formation. The exact mechanism for CSF production is not fully understood. In order to study this mechanism from the enzyme histochemical standpoint, the previously reported studies are reviewed, in addition to the authors' own electron microscopic enzyme histochemical observations on this tissue. The ultrastructure and enzyme biochemistry of choroid plexus epithelial cells are considered, together with the histochemistry of the following enzymes: alkaline and acid phosphatase, Mg^{2+}-ATPase, Na^+, K^+-ATPase, glucose-6-phosphatase, thiamine pyrophosphatase, adenylate cyclase, carbonic anhydrase, oxidoreductase, esterase, several hydrolases, and other enzymes. Finally, CSF formation and active transport in the choroid plexus epithelial cells are discussed, mainly in terms of the results of our enzyme cytochemical observations on Na^+, K^+-ATPase and carbonic anhydrase in this tissue.

INTRODUCTION

The functional activities of the choroid plexus and the nature of the blood cerebrospinal fluid barrier have been investigated by morphological, physiological, biochemical and histochemical studies. It is generally accepted that the choroid plexus plays a major role in the production and regulation of CSF, although all CSF is not elaborated from it. The actual mechanisms involved are still poorly understood. Pharmacophysiological experiments have suggested a relationship to the activity of certain enzymes. A large increase in CSF production was demonstrated after the intraventricular administration of cholera toxin which stimulates adenylate cyclase (Epstein *et al.*, 1977). Production was reduced when ouabain was introduced as a Na^+, K^+-ATPase inhibitor (Welch, 1963; Vates *et al.*, 1964; Cserr, 1965; Ames *et al.*, 1965*b*; Holloway and Cassin, 1972; Smith *et al.*, 1974), and when acetazolamide was introduced as a carbonic anhydrase inhibitor (Tschirgi *et al.*, 1954; Kister, 1956; Knopp *et al.*, 1957; Elvidge *et al.*, 1957; Atkinson and Ward, 1958; Birzis *et al.*, 1958; Fisher and Copenhaver, 1959; Davson and Spaziani, 1962; Davson and Pollay, 1963; Pollay and Davson, 1963; Welch, 1963; Oppelt *et al.*, 1964; Ames *et al.*, 1965*b*; Rubin *et al.*, 1966; Davson and Segal, 1970; Davson, 1972; Holloway and Cassin, 1972; Smith *et al.*, 1974).

Metabolic studies on the choroid plexus have revealed it to be rich in enzymes necessary for active transport, and biochemical analyses of the choroid plexus have indicated that the general metabolic activity per unit weight is one third to one half the value for the kidney (Fisher and Copenhaver, 1959).

The rapid development of enzyme histochemical techniques has resulted in the localization of several enzymes in the cells of the choroid epithelium, not only at the level of light microscopy, but also by electron microscopy, although these studies have been few in number. Torack (1965) investigated the enzyme histochemistry of the choroid epithelial cells by electron microscopy and attempted to demonstrate relationships between biochemical activity and the ultrastructural components so that a morphological and functional correlation of cellular activity could be defined. Localization of enzymes is essential for a clear understanding of cell activity and interaction.

By the use of histochemical techniques, the following enzymes have been localized in the choroid plexus epithelium by light microscopy. These are alkaline phosphatase (ALPase) (Landow *et al.*, 1942; Wislocki and Dempsey, 1948; Shimizu, 1950; Leduc and Wislocki, 1952; Chiquoine, 1954; Fisher and Copenhaver, 1959; Kaluza *et al.*, 1964; Bartoníček and Lojda, 1964; Cancilla *et al.*, 1966; Shantha and Manocha, 1968; Manocha, 1970), acid phosphatase (ACPase) (Wislocki and Dempsey, 1948; Shimizu, 1950; Naidoo and Pratt, 1951; Leduc and Wislocki, 1952; Becker *et al.*, 1960; Anderson and Song, 1962; Bartoníček and Lojda, 1964; Kaluza *et al.*, 1964; Shantha and Manocha, 1968; Manocha, 1970), adenosine triphosphatase (Becker *et al.*, 1960; Bartoníček and Lojda, 1964; Kaluza *et al.*, 1964; Cancilla *et al.*, 1966; Shantha and Manocha, 1968; Manocha, 1970), carbonic anhydrase (CAHase) (Korhonen *et al.*, 1964; Roussel *et al.*, 1979), γ-glutamyl transpeptidase (Albert *et al.*, 1966), succinic dehydrogenase (Leduc and Wislocki, 1952; Kaluza *et al.*, 1964; Shantha and Manocha, 1968), thiamine pyrophosphatase (TPPase) (Bartoníček and Lojda, 1964; Cancilla *et al.*, 1966; Shantha and Manocha, 1968), cytochrome oxidase (Kaluza *et al.*, 1964; Shantha and Manocha, 1968), lactic dehydrogenase (Kaluza *et al.*, 1964; Cancilla *et al.*, 1966; Shantha and Manocha, 1968), di- and triphosphopyridine nucleotide tetrazolium reductase (DPNH-T, TPNH-T reductase) (Becker *et al.*, 1960; Kaluza *et al.*, 1964), nonspecific esterase (Leduc and Wislocki, 1952; Bartoníček and Lojda, 1964; Shantha and Manocha, 1968), glyceraldehyde-3-phosphate-hydrogenase (Kaluza *et al.*, 1964), indoxyl esterase (Fishman and Hayashi, 1962), certain phosphatases (Bourne, 1958), β-glucuronidase (Kroh and Renkawek, 1973), N-acetyl-β-D-glucosaminidase (Davidoff and Galabov, 1976), choline esterase (Joó and Csillik, 1966; Shantha and Manocha, 1968), monoamine oxidase (Shantha and Manocha, 1968), phosphorylase (Shimizu and Okada, 1957), aminopeptidase (Bartoníček and Lojda, 1964), glucose-6-phosphatase (Shantha and Manocha, 1968), aldolase (Shantha and Manocha, 1968), DPN-diaphorase (Shantha and Manocha, 1968), glucose-6-phosphate dehydrogenase (Shantha and Manocha, 1968), AMPase (Bartoníček and Lojda, 1964) and ADPase (Bartoníček and Lojda, 1964).

Very few enzymes have been localized in the choroid plexus by electron microscopy. These are ACPase (Matano and Ishii, 1967; Masuzawa *et al.*, 1981*c*), ALPase (Ishii and Matano, 1968; Masuzawa *et al.*, 1980), Na^+K^+-ATPase (Matano and Ishii, 1973; Milhorat *et al.*, 1975), p-nitrophenyl phosphatase (Masuzawa *et al.*, 1981*a*), Mg^{2+}-ATPase (Torack and Barrnett, 1964; Masuzawa *et al.*, 1980), adenylate cyclase (Masuzawa *et al.*, 1981*a*), glucose-6-phosphatase (Masuzawa *et al.*, 1981*c*), thiamine pyrophosphatase (Masuzawa *et al.*, 1981*c*) and carbonic anhydrase (Masuzawa *et al.*, 1981*d*).

The purpose of the present paper is to describe localization of enzyme activity in the choroid plexus, both as reported in the literature and from the authors' own observations. From the authors' localization of enzyme activity, the function of the choroid plexus is discussed, especially as a secretory epithelium.

ULTRASTRUCTURE OF THE CHOROID PLEXUS EPITHELIUM

The choroid plexus is a highly vascularized villous structure, covered by a single layer of cuboidal cells having specialized apical or ventricular surfaces.

Since the initial observations on the ultrastructure of the rat choroid plexus by Dempsey and Wislocki (1955) and Van Breemen and Clemente (1955), ultrastructural findings in many other species have been reported, including the rat (Maxwell and Pease, 1956; Wislocki and Ladman, 1958; Nakamura *et al.*, 1975), monkey (Wislocki and Ladman, 1958), man (Bargmann and Katritsis, 1966; Dohrmann and Bucy, 1970), cat (Maxwell and Pease, 1956), mouse (Dohrmann and Herdson, 1969), guinea pig (Case, 1959), rabbit (Maxwell and Pease, 1956; Millen and Rogers, 1956; Wislocki and Ladman, 1958; Tennyson and Pappas, 1961; Pappas and Tennyson, 1962; Witzel and Hunt, 1962) and frog (Maxwell and Pease, 1956; Pontenagel, 1962).

The cuboidal epithelial cells have an apical microvillous border. Microvilli are membrane-bound cytoplasmic projections which can be classified into two types: one is a symmetrical, finger-like structure, while the other (clavate microvillus) is relatively shorter, rounded or club-shaped (Dohrmann and Bucy, 1970). Occasional cilia can be seen as a persistent embryological remnant along the microvillous surface and the number of these per epithelial cell varies.

Tight junctions (Farquhar and Palade, 1963) on the ventricular surface join one epithelial cell to another. The basal plasma membrane, which rests on the basement membrane and is sited in the vicinity of the intercellular junctions, shows infoldings. The space between the choroidal basement membrane and the capillaries of the choroid plexus is filled with a loose connective tissue stroma composed primarily of fibroblasts along with variable amounts of collagen fibrils (Carpenter, 1966).

The intracellular organelles of epithelial cells include numerous elongated mitochondria dispersed throughout the cytoplasm, a large ovoid nucleus which is centrally situated, the Golgi complex which is located in a paranuclear position, lysosomes, occasional lipid droplets, a few multivesicular bodies, pinocytotic vesicles which are most concentrated in the cytoplasm adjacent to the plasma membrane or microvillous border and rough or smooth endoplasmic reticulum. Most choroid plexus papillomas closely mimic the architecture of the normal choroid plexus and behave as benign neoplasms (Masuzawa *et al.*, 1981*b*, 1982).

The capillaries of the choroid plexus consist of a thin endothelium resting on a definite basement membrane. The cytoplasm of the endothelial cells is extremely attenuated, fenestrated or characteristically perforated.

STUDIES ON ENZYME BIOCHEMISTRY IN THE CHOROID PLEXUS

The activity of the enzymes and their roles in choroid plexus metabolism have been the subject of previous studies. Krebs and Rosenhagen (1931) found that the surviving choroid plexus of the cat exhibited a rate of oxygen consumption comparable to that of parenchymatous organs such as the liver and kidney.

In the cat, the quantity of CSF which flows through the aqueduct of Sylvius per day has been found to be 12 ml, based on an average weight of 30 mg for the choroid plexuses of the lateral and third ventricles (Flexner and Winters, 1932). Consequently, the free energy change per mg of plexus per day was about 0.005 calories, and CSF was considered not as a dialysate or an ultrafiltrate, but rather as a secretion, implying the exercise of metabolic work by the cells in the formation of the fluid (Flexner, 1934).

Stiehler and Flexner (1938) described how the reversible oxidation reduction system of the barrier between the stroma and the epithelium in the choroid plexus provides the source of energy for CSF secretion. The work of Stiehler and Flexner was further advanced by Friedenwald *et al.* (1942) who studied the biochemical activity of various dehydrogenases in the choroid plexus.

High glucose consumption is one of the characteristic features of the choroid plexus. Glucose is an essential nutritional factor, especially for the energy requirement for CSF secretion. In the normal cerebrum, neurons display the highest succinic dehydrogenase activity, followed by choroidal epithelium and ependymal cells (Ogawa and Zimmerman, 1959). Oxidative enzymes have been shown to be concentrated primarily in the ependymal rather than the vascular (plexus *per se*) or connective tissue cells of the choroid plexus (Quay, 1960). In studies of the effects of various substrates, the O_2 uptake of ependymal layers of the fourth ventricle of the rat was greatest with glucose, pyruvate, mannose and lactic acid. The presence of glucose led to maximal O_2 uptake by the choroid plexus with 125 mM Na^+ and 19 mM K^+ in the medium. The respiration of the ependymal layer was increased by small amounts of Ca^{2+}, Mg^{2+} and increasing amounts of PO_4^{2-} ($0 \sim 45$ mM), and inhibited by Cu^{2+} (Quay, 1963). Numerous mitochondria were concentrated at the apical end of the choroidal epithelium, which correlates with the very high O_2 consumption of the epithelium in that region (Quay, 1966).

Biochemical analysis of the cat's choroid plexus by Fisher and Copenhaver (1959) indicated that the general metabolic activity per unit weight was one third to one half the value for the kidney, and that alkaline phosphatase, carbonic anhydrase, choline esterase and β-glucuronidase might figure in active transport in the epithelium (Table).

It has been reported that the inhibition of carbonic anhydrase by acetazolamide alters the formation and the electrolyte composition of CSF (Tschirgi *et al.*, 1954). The principal change was decreased Cl^- concentration (Maren and Robinson, 1960). Quantitative determination of carbonic anhydrase in single cells with the Cartesian diver technique of Linderström-Lang (1937) demonstrated that in the rat this enzyme was concentrated in the glial and choroidal cells, and the quantity of this enzyme was estimated at 18×10^{-20} mol of enzyme per cell, and a single cell of the choroid plexus at 300×10^{-20} mol of enzyme per cell (Giacobini, 1961) (Table). In the rabbit, carbonic anhydrase activity was higher in the choroid plexus of the fourth ventricle than that of the lateral ventricle, and depletion of noradrenaline from the adrenergic nerves by reserpine increased carbonic anhydrase activity (Edvinsson *et al.*, 1974).

Epstein et al. (1977) demonstrated a large increase in CSF formation after the intraventricular administration of cholera toxin through stimulation of the adenylate cyclase-cyclic AMP pathway in the choroid plexus and periventricular compartment.

Bonting *et al.* (1961) reported Na^+, K^+-ATPase activity in various tissues of the cat, among which the activity of the choroid plexus was 0.098 mmol ATP split/g wet

TABLE. BIOCHEMICAL ENZYME ACTIVITY IN THE CHOROID PLEXUS

Enzymes		
Succinic dehydrogenase		
(Fisher and Copenhaver, 1959)	Cat	5.760 ± 380 μl O_2/h/g
Cytochrome oxidase		
(Fisher and Copenhaver, 1959)	Cat	25.50 ± 1410 μl O_2/h/g
Alkaline phosphatase		
(Fisher and Copenhaver, 1959)	Cat	1.767 ± 96 μmol p-nitrophenyl phosphate split/h/g
Choline esterase		
(Fisher and Copenhaver, 1959)	Cat	19.3 ± 3.7 μmol acetylthiocholine split/h/g
β-glucuronidase		
(Fisher and Copenhaver, 1959)	Cat	950 ± 77 μg phenolphthalein glucuronidase split/h/g
Carbonic anhydrase		
(Fisher and Copenhaver, 1959)	Cat	179 ± 12 Ashby units/g tissue
(Giacobini 1961)	Rat	300×10^{-20} mol of enzyme/cell (a single cell of the tissue) or 15×10^{-23} mol of enzyme/μ^3 (unit volume)
Na^+, K^+-ATPase		
(Bonting *et al.*, 1961)	Adult cat	0.098 mmol ATP split/g wet weight/h, at 37° C
(Miwa *et al.*, 1980)	Adult rabbit	1.7 ± 0.6 μmol pi/mg protein/h
Mg^{2+}-ATPase		
(Miwa *et al.*, 1980)	Adult rabbit	8.3 ± 1.2 μmol pi/mg protein/h
HCO_3-ATPase		
(Miwa *et al.*, 1980)	Adult rabbit	2.0 ± 0.3 μmol pi/mg protein/h

weight/h incubation at 37° C and measured 6.5 per cent cerebral grey matter activity (Table). Miwa *et al.* (1980) investigated the properties of ATPase in the choroid plexus of the cerebral ventricles in the rabbit using tissue homogenates. They noted that Na^+, K^+-ATPase activity in the choroid plexus was significantly lower than that in the brain, and that HCO_3-ATPase activity in the choroid plexus was significantly lower than that in the kidney, while Mg^{2+}-ATPase in the choroid plexus was higher than that in the brain and kidney. They further demonstrated that there was no significant difference among the choroid plexuses of the lateral, third and fourth ventricles in terms of Na^+, K^+-ATPase and HCO_3-ATPase activity.

ENZYME HISTOCHEMISTRY IN THE CHOROID PLEXUS EPITHELIUM

Alkaline Phosphatase (*E.C.3.1.3.1*)

Alkaline phosphatase (ALPase) is the same as phosphomonoesterase which works on the alkaline side of neutrality, particularly at pH 9.0 and above. It is possible that the activity of ALPase is concerned with the transfer of phosphate from one alcohol to another (London and Hudson, 1955).

The first clear historical recognition of an enzyme by histochemistry was ALPase, which Takamatsu (1939) and Gomori (1939) independently succeeded in demonstrating in tissue sections by using the metal precipitating method. The other method for the histochemical demonstration of ALPase is the azo dye method which was developed by Menten *et al.* (1944).

Since Wislocki and Dempsey (1948), several reports of ALPase activity in the choroid plexus by light microscopy have appeared. For the study of this enzyme activity, Wislocki and Dempsey (1948) employed the modified version of Gomori's method (Dempsey and Deane, 1946) using yeast nucleic acid, glycerophosphate and fructose diphosphate as substrate in the incubation medium. The reaction was localized patchily in the walls of the choroidal capillary vessels and adjacent stroma. Shimizu (1950) reported that with the exception of rabbit and chicken tissue, ALPase activity was mainly confined to the connective tissue stroma and the endothelium of the capillaries, and was absent or at least very weak in the epithelium of mice, rats and guinea pigs as evidenced by a modification of the technique of Takamatsu and Gomori. Intense reactions in the stroma and perivascular sheath of the capillaries and some activity in the epithelial cells of the choroid plexus were observed by Leduc and Wislocki (1952) with the modified method of Gomori (Dempsey and Deane, 1946). In the choroid plexus of the cat, Fisher and Copenhaver (1959) demonstrated the highest concentrations of ALPase in the choroidal capillary walls using Gomori's method (1951). Kaluza *et al.* (1964), using the azo dye method of Burstone (1958, 1959), found ALPase activity in the stroma, and noted an increase in activity from the 35th to the 46th stages of development in the chick embryo. Cancilla *et al.* (1966), using Gomori's modified technique (Becker *et al.*, 1960), reported that blood vessel activity was present in the choroid plexus of the fetal rat and that this activity continued into adult life. However, no activity was found in the epithelial cells of the choroid plexus. According to Manocha (1970), who used Gomori's calcium cobalt method (1939, 1951) and an α-naphthyl phosphate method, mild ALPase activity was concentrated in the epithelial lining cells of the choroid plexus of the squirrel monkey. He observed more pronounced ALPase activity at the luminal border and moderately strong activity in the blood vessels.

Most of the findings obtained by light microscopy localized the activity of ALPase in the connective tissue stroma and endothelium of the capillaries, with little or no activity in the cytoplasm of the choroidal epithelial cells. No other details had been reported before the application of ultracytochemistry to this enzyme.

Within the limits of light microscopic histochemistry of alkaline phosphatase, it was undecided whether the nuclear staining reflected a true or an artificial localization of the enzyme. Some researchers maintained that the nuclear reaction for ALPase in various tissues was artefactual (Albert, 1955; Waked and Kerr, 1955; Silva-Pinto and Coimbra, 1963). Mizutani (1969) reported that nonspecific lead precipitation occasionally occurred around the pores of the nuclear envelope. On the other hand, other workers believed that ALPase activity did exist in nuclei (Shimizu, 1950; Bourne, 1958; Cox and Macleod, 1962; Feigin and Wolf, 1955; Griffin *et al.*, 1967; Tewari and Tyagi, 1968; Tewari and Sood, 1969). Franke and his associates (1970), from biochemical studies, found a trace of ALPase activity in the nuclear membrane and nuclear fractions, and by ultrastructural cytochemistry, the possible presence of ALPase in the nuclear envelope (Makita and Sandborn, 1970) and in the nuclear pores (Cutler *et al.*, 1974) was demonstrated. Nevertheless, in spite of these reports, on the basis of their histochemical studies on the choroid plexus epithelial cells by the use of the lead citrate method (Ogawa *et al.*, 1967), the authors have the impression that nuclear or nuclear membrane staining from alkaline phosphatase activity does not occur. This is the most reliable technique at present (Masuzawa *et al.*, 1980).

The conventional incubating medium for alkaline phosphatase containing 'lead nitrate' forms precipitates at an alkaline pH. This was the reason for incubation at pH 7.2 to 7.6 with or without potassium sodium tartrate as a chelating agent (Ogawa *et al.*, 1967).

It was Brandes *et al.* (1956) who demonstrated, for the first time, ALPase activity in the intestine by electron microscopy. The ultrastructural localization of this type of enzyme activity in the brain has proved to be quite difficult with the cobalt sulphide reaction produced by Gomori's method. The preservation of cerebral fine structure was excellent if the reaction was performed at pH 9.0 on tissue fixed in glutaraldehyde, but the localization of the cobalt sulphide was no longer specific (Torack, 1965). To avoid this dilemma, efforts towards the visualization of ALPase activity at the electron microscopical level have been continued, including the use of the lead nitrate method of Möelbert *et al.* (1960). The lead citrate method, in which lead citrate, which is readily soluble at high pH, is employed as a precipitating reagent, was divised by Ogawa *et al.* (1967). At present, this method is the most widely used and is judged to be the most reliable.

Ishii and Matano (1968), demonstrated ALPase ultracytochemically in the rat choroid plexus epithelium at the sites of the plasma membrane of the microvilli and basal infoldings, at the junctions between epithelial cells, in the fibrocytes of the stroma and in the endothelial cells of the capillary wall. They observed no positive reaction for this enzyme in the cytoplasm.

The authors (Masuzawa *et al.*, 1980) employed the lead citrate method (Ogawa *et al.*, 1967) for the electron microscopical localization of ALPase in the choroid plexus epithelium of the rat. Electron-dense reaction products were found only along the basal plasmalemmas (fig. 1). There were no reaction products along the apical

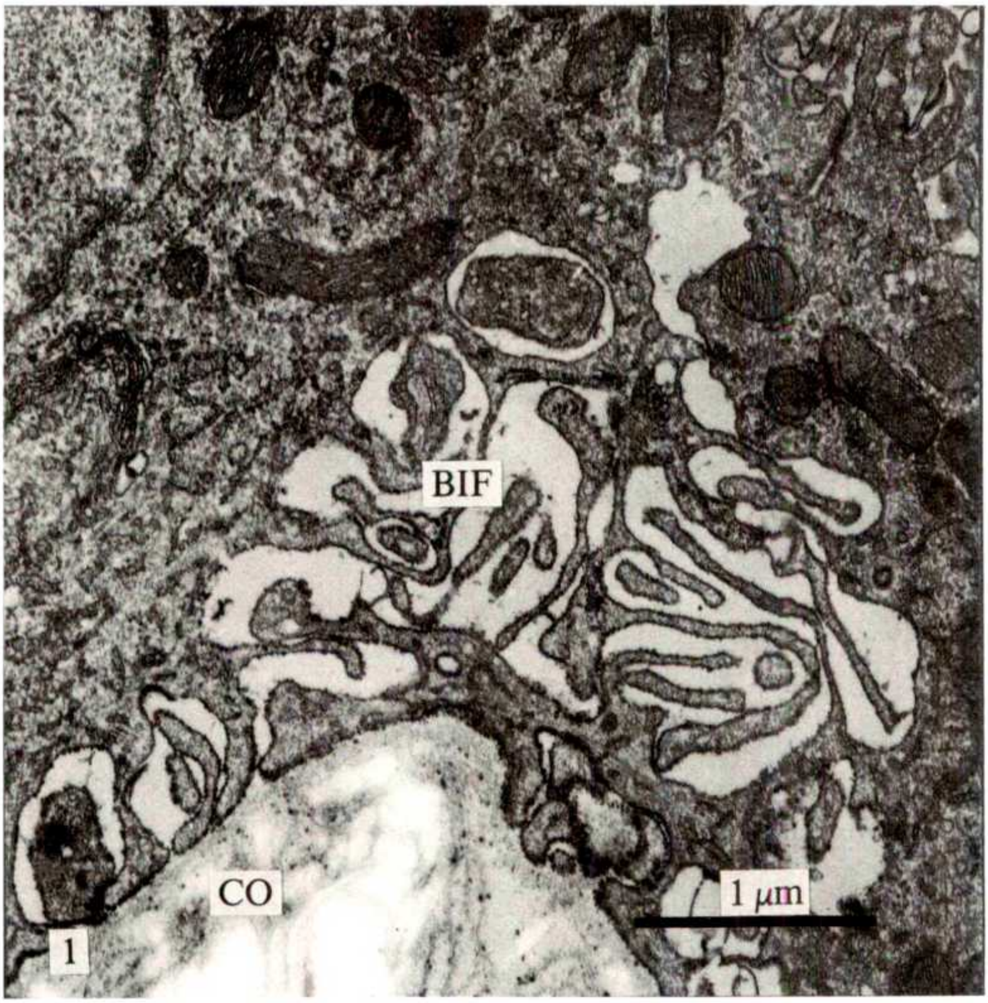


FIG. 1. Alkaline phosphatase activity in rat choroid plexus epithelial cells. Electron-dense reaction products are found along the basal infoldings (BIF) and diffusely in the connective tissue (CO).

(including the microvilli) or lateral plasmalemmas nor in the cytoplasm. The capillary endothelium showed reaction products in the wall. In the control experiments, these electron-dense reaction activities were completely inhibited when bromotetramisole (Borgers, 1973) was added at a final concentration of 0.5 mM.

The role of ALPase in the choroid plexus. ALPase, although a common enzyme which exists in most tissues, has not been fully elucidated, either in terms of its role or its mechanism of action. It is possible that ALPase in the intestine, kidney and secretory glands (Möelbert *et al.*, 1960; Reale, 1962; Mizutani and Barrnett, 1965; Bogart, 1968; Hugon and Borgers, 1968), in the neuropil of the brain (Landow *et al.*, 1942; Shimizu, 1950) and in the capsular cells of ganglia (Tewari and Bourne, 1964) might participate in transmembrane transport.

Wislocki and Dempsey (1948) discussed the presence of ALPase activity in cerebral vessels in relation to the blood-brain barrier, and suggested that this enzyme might control the passage of phosphate-containing substances and might provide protection from certain noxious substances. The distribution of ALPase activity within the nervous system was generally such that a highly active zone was invariably interposed between blood or body fluid and a nerve cell. Shimizu (1950) indicated that ALPase might have some relation to the passage of various substances between the blood and brain tissue. Samorajski and McCloud (1961) similarly endorsed the role played by ALPase in the blood barrier mechanism and in the transport of various chemicals and nutrients through the membranes of blood vessels. Djuričič *et al.* (1978) speculated that the role of ALPase in isolated brain microvessels and brain parenchyma was probably in preventing the entry of phosphate esters into brain tissue and/or participating in transphosphorylation processes.

In the choroid plexus, ALPase activity was localized by electron microscopy to the endothelium of capillaries and along the cell membranes, especially along the basal plasmalemma facing the capillaries. An analogous role or mechanism for ALPase could therefore be considered when compared with the cerebral microvessels. In their histochemical and biochemical studies, Fisher and Copenhaver (1959) considered ALPase to be one of the enzymes which might play a role in active transport in the choroid plexus. Ishii and Matano (1968), from their observations on the ultrastructural localization of ALPase and ACPase in the choroid plexus, focused on the plasma membranes of the microvilli and of the basal infoldings in relation to the function of the choroid plexus as part of the blood-CSF barrier.

Acid Phosphatase (E.C.3.1.3.2)

To determine the localization of acid phosphatase (ACPase) activity at the level of light microscopy, the metal salt method was developed by Gomori (1941, 1950) and another method, the azo dye method, was introduced by Barka and Anderson (1962). It was Sheldon *et al.* (1955) who first demonstrated this enzyme by electron histochemistry. The cytochemistry of ACPase had been developed by several researchers and this enzyme has become recognized as a marker enzyme of lysosomes.

In the choroid plexus, the enzyme histochemistry of ACPase activity as revealed by light microscopy has been documented since Wislocki and Dempsey (1948) who, after treatment with glycerophosphate at pH 5 for 72 h incubation, demonstrated activity of ACPase in monkey tissue. This involved mainly the nuclei but also to some extent the cytoplasm of the choroidal cells and, to a much lesser extent, the stroma and blood vessels. Shimizu (1950), in describing ACPase activity in the choroid plexus of the rabbit, noted that the nuclei and cytoplasm of the epithelial cells were distinctly positive, but the connective tissue and vascular endothelium were negative, using sodium glycerophosphate as a substrate and a 24 h incubation at pH 4.8. Naidoo and Pratt (1951) applied Gomori's method for ACPase to freeze-dried paraffin-embedded tissue. Both the vasculature and the epithelium of the choroid plexus stained deeply. Nuclear staining of the ependymal cells was more prominent than that of the cytoplasm. Leduc and Wislocki (1952) used Gomori's modified technique (Dempsey and Deane, 1946) and the epithelium of the rat choroid plexus showed a strong reaction, mainly present in the nuclei.

Until the report by Becker *et al.* (1960), attempts to confirm ACPase localization in lysosomes had failed. It was believed that the nuclear staining was significant. Gomori's lead phosphate precipitation technique (Gomori, 1941) has been used almost exclusively in the many histochemical studies of ACPase distribution in the nervous system. Nuclear staining artefact, specific nonenzymatic precipitates, prolonged incubation times and diffusion of the reaction products were major disadvantages of this technique. The azo dye method, especially using hexazonium pararosanilin, was considered as one of the suitable methods for the demonstration of ACPase activity in neural tissue. This showed no nuclear staining (Anderson and Song, 1962). Becker *et al.* (1960) applied the Gomori method (1950) for ACPase and considerable staining was present in the rat choroid plexus epithelium where the enzyme activity was localized in cytoplasmic bodies, varying in size from 0.3 to 0.7 μm and blackened by accumulated lead sulphide. These were presumed to be lysosomes. Nuclear and nucleolar staining were uncommon and inconstant.

Kaluza *et al.* (1964) employed the azo dye method of Burstone (1958, 1959) for the visualization of ACPase activity in the choroid plexus of chick embryos. The enzyme was found in the brush borders of the epithelial cells of the choroid plexus of a 9-day chick embryo. All nuclei were invariably unstained. On the inner walls of the epithelial cells, the granules were sparsely distributed. Of interest was the fact that an increase of ACPase was seen in the epithelium, but a decrease in the ependymal cells. The distribution of ACPase in the developing rat choroid plexus was studied by Cancilla *et al.* (1966) with the modified Gomori technique (Becker *et al.*, 1960). In all age groups choroidal cell activity was localized to discrete cytoplasmic bodies, 0.2 to 0.8 μm in diameter, which were presumed predominantly to be lysosomes. Most of the lysosomes were located in the basal and perinuclear zones. This localization was unaffected by age. However, in fetal rats the sites of activity were relatively few in comparison with post-partum animals, in which their number increased rapidly within the first week and reached a maximum at 30 days. Adult rats tended to have fewer lysosomes than weanling (30 day) rats.

Using the Gomori method (1950) and azo dye method (Barka and Anderson, 1962), Manocha (1970) noted that the epithelial lining cells of the choroid plexus of the monkey showed intensely strong ACPase activity.

Although there have been some histochemical reports in favour of nuclear staining related to ACPase activity (Tewari and Sood, 1967; Dabholkar and Tewari, 1968; Sood and Tewari, 1969), others have expressed the opinion that the nuclear reaction for ACPase was artefactual and nonspecific (Albert, 1955; Olsen and Petri, 1963; Silva-Pinto and Coimbra, 1963; Masuzawa *et al.*, 1981*c*). Franke and his associates (1970) interpreted their values with ACPase in the nuclear (membrane) fractions as an indication of lysosomal contamination in spite of earlier remarks on microsomal and nuclear (membrane) ACPase activity.

Very little has been reported concerning the ultrastructural localization of this enzyme in the choroid plexus epithelial cells. Matano and Ishii (1967) demonstrated ACPase activity in the plasma membranes of the microvilli and of the basal infoldings of the epithelium in the rat, as well as in lysosomes, by Gomori's modified method. The authors (Masuzawa *et al.*, 1981*c*), using Gomori's method (1950) with β-glycerophosphate as substrate, noted that the sites of ACPase activity were limited to lysosomes (fig. 2A) and the inner Golgi cisternae (fig. 2B) and were not present elsewhere. No activity was detected in the plasmalemmas of the choroidal epithelial cells. Miyayama *et al.* (1975) observed dual localization of ACPase in lysosomal and extralysosomal sites of the tubule epithelial cells of normal mouse kidney by light and electron microscopy using a modified Gomori's method lead-salt with p-nitrophenylphosphate as substrate.

The role of ACPase in the tissue. Based on an enzyme histochemical study, Shimizu (1950) pointed out that the distribution of ACPase in the nervous system differed from that of ALPase in certain important respects. Unlike ALPase, ACPase is absent in the vascular endothelium and in the stroma of the choroid plexus. It was found in the epithelium of the choroid plexus and, in large amounts, in the arachnoid membrane.

The meaning of the polarized distribution of lysosomes in the cells of the choroid plexus was not clear; nor was their large size and apparently high level of ACPase activity. It was suggested that this might be related to the uptake of materials from the CSF or to the storage of the waste products of cell metabolism (Becker *et al.*, 1960). According to Manocha (1970), the strong ACPase activity in the choroid plexus might be concerned with a secretory function. A comparative study of the neurons in different areas of the brain showed that the ACPase reaction was less variable than the activity of succinic dehydrogenase or lactic dehydrogenase (Manocha and Bourne, 1966*a*, *b*, *c*; 1968; Manocha *et al.*, 1967*a*, *b*). This supported the assumption that ACPase was more related to static maintenance metabolism of the cells than to dynamic functional metabolism.

Acid phosphatase is accepted as a marker enzyme of lysosomes which are known to be involved in multiple ways in the phenomena of intracellular digestion. Morphologically, lysosomes show a striking polymorphism in form and size. The cytochemical test for ACPase activity invariably serves as an excellent marker for lysosomes, and it has contributed significantly to the understanding of that great variety of morphologically different structures which are identified as lysosomes (Saito, 1979).

Magnesium-activated Adenosine Triphosphatase

Adenosine triphosphatase (ATPase) (E.C.3.6.1.3) liberates inorganic phosphate from ATP. ATPase activity is observed in myosin and actomyosin, mitochondria,

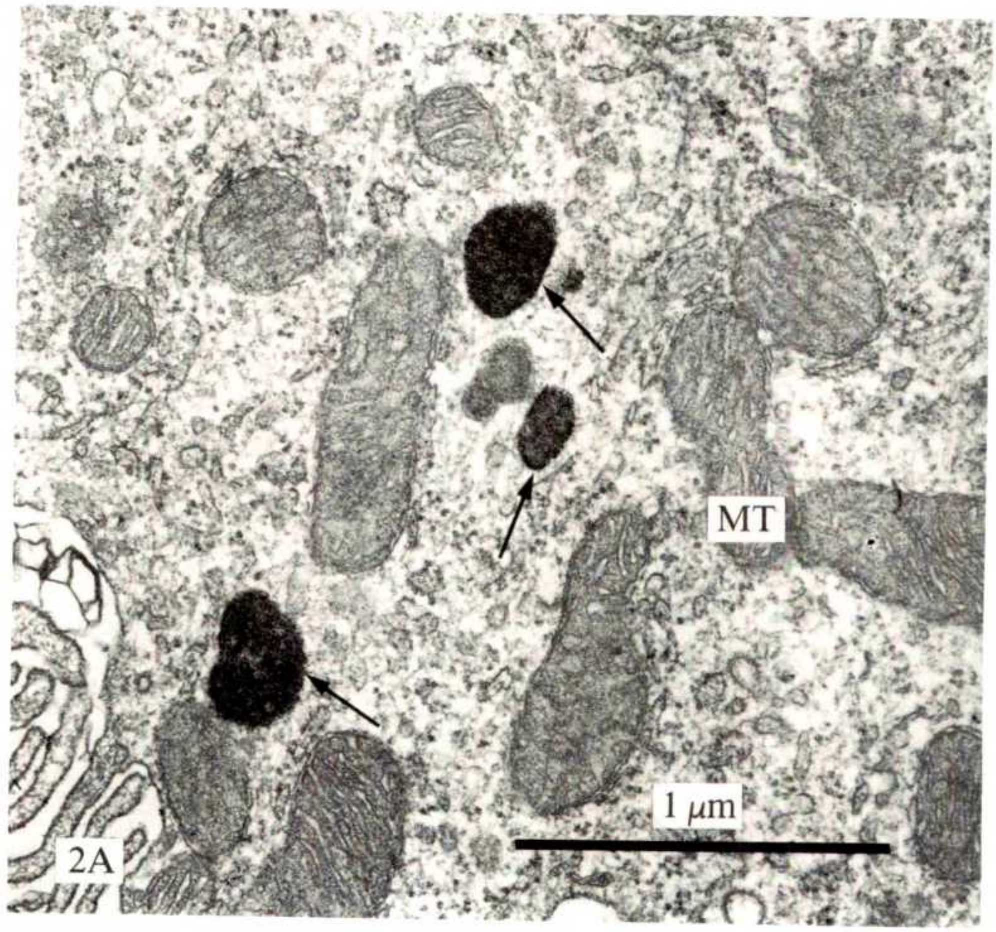
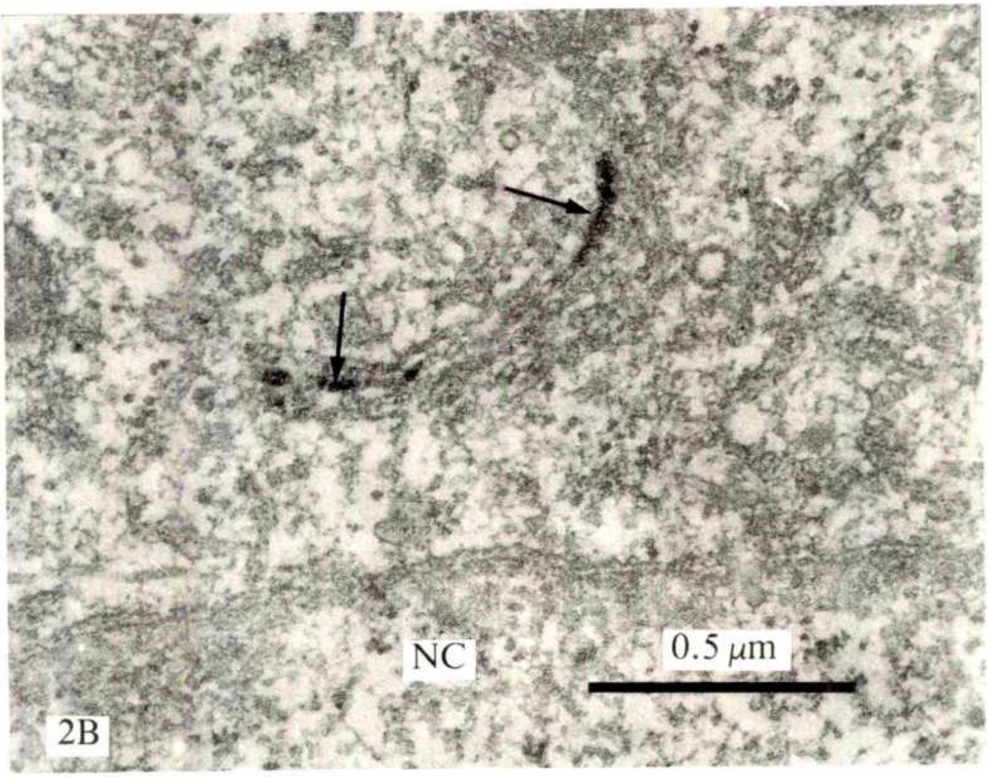


FIG. 2. Acid phosphatase activity in rat choroid plexus epithelial cell. A, the electron-dense reaction products are demonstrated in lysosomes (arrows). No reaction is seen in mitochondria (MT). B, some electron-dense reaction products are found in Golgi cisternae (arrows). No reaction is seen in the nucleus (NC).

microsomes and cell membranes. The enzymes separate mainly into the calcium-activated myosin ATPase, the magnesium-activated mitochondrial and cell membrane-localized ATPase, and the sodium potassium-activated ATPase which is the enzymatic equivalent of the system responsible for active transmembrane sodium transport. The histochemistry for the sodium potassium-activated ATPase will be dealt with in the next section.

For the histochemical detection of calcium-activated myosin-ATPase, the Padykula and Herman method (1955*a*) with ATP as a substrate and $CaCl_2$ as a capturing reagent is suitable. Unfortunately the calcium ions are too weak to be visualized as an electron-dense reaction product at the ultrastructural histochemical level. Activity of myofibrillar ATPase in the A band was demonstrated histochemically at a fine structural level in cardiac myofibrils in the rat, using a lead precipitation technique and either Ca^{2+} or Mg^{2+} as the activating ion (Tice and Barrnett, 1962*a*).

Attempts have been made to visualize the activity of the magnesium-activated mitochondrial ATPase. The precise intramitochondrial localization of this ATPase activity is controversial and unresolved. Ogawa and Mayahara (1969), by the use of lead citrate as the capturing reagent and a sodium salt of ATP as substrate, found



ATPase activity in the form of linearly arranged particles associated with the inner membrane of normal rodent cardiac mitochondria.

Here the description is limited to the histochemical localization of the magnesium-activated and cell membrane-localized ATPase. Mg^{2+}-ATPase activity is seen only in the presence of Mg^{2+} alone and is not particularly dependent on any other cations. It requires Mg^{2+} and ATP on the inner surface of the membrane. It is found in membrane preparations from many sources in addition to the red blood corpuscle and is often considered, implicity at least, to be a 'background' activity, probably because its function is unknown (Vincenzi and Hinds, 1976).

For the histochemistry of Mg^{2+}-ATPase, the two well-known methods are those of Wachstein and Meisel (1957) with lead nitrate as a capturing reagent at pH 7.2, and Ogawa and Mayahara (1969) with lead citrate as a capturing reagent at alkaline pH.

According to Manocha (1970), adenosinetriphosphatase activity was in general present in the neuropil and blood vessels. In the neurons, the perikarya usually show a mild reaction, whereas the cell membrane produces a significant reaction. The substitution of adenosine diphosphate for ATP in the incubation results in absence of activity in the plasma membranes of nerve cell bodies and dendrites (Becker *et al.*, 1960).

The light microscopical histochemistry of ATPase has been reported by several researchers. Naidoo and Pratt (1951) demonstrated ATPase activity in the choroid plexus, both in blood vessels and epithelium. Becker *et al.* (1969), using the Wachstein-Meisel method, showed that in the epithelial cells of both the ependyma and the choroid plexus of the rat, the cell membranes were deeply stained. Kaluza *et al.* (1964) studied the localization of ATPase and found that at the 35th stage of development there was moderate cytoplasmic activity and the brush borders of the epithelial cells were sharply outlined. At the 40th stage of development, the distribution was limited to the brush borders, and in the 21-day-old chick, ATPase was distributed throughout the cytoplasm with lower activity of the brush border, as is seen in the choroid plexus in the 40th stage of development.

Cancilla *et al.* (1966) also described this enzyme activity in the blood vessels of the fetal rat choroid plexus and observed a reaction product on the ventricular surface of the choroidal cells in addition to the blood vessels in the choroid plexus of the weanling rat. Shantha and Manocha (1968) and Manocha (1970), using the Wachstein-Meisel technique, demonstrated ATPase activity which was strong in both the stroma and in the lining choroidal epithelial cells. The nucleus in particular gave a strong reaction and, in their preparations, enzyme activity tended to concentrate at the peripheral part of the cytoplasm towards the luminal border.

Some nuclear and particularly nucleolar reactions might represent nonspecific absorption of Pb^{2+} and not be truly enzymatic as indicated by Adams (1965).

The ultrastructural localization of ATPase in the choroid plexus epithelial cells has been studied by several investigators. Torack and Barrnett (1964), using the Wachstein-Meisel technique, noted that the choroid plexus displays considerable

ATPase activity, localized to the epithelial cells. In the blood vessels, the basement membrane was found to be devoid of enzyme activity and only one zone of enzyme activity was localized in the endothelial cells.

Torack and Barrnett (1964) incubated the rat choroid plexus epithelium in Wachstein-Meisel medium using ATP as a substrate. They noted that the surface of numerous villi, including the apical plasmalemma of the epithelial cells and capillary basement membranes, did not display ATPase activity; however, at the outer basal surfaces and at the cellular interfaces of these epithelial cells, a granular reaction product was deposited in scattered foci.

Masuzawa *et al.* (1980) demonstrated Mg^{2+}-ATPase activity in the rat choroid plexus by the Wachstein-Meisel method. The electron-dense reaction products of this enzyme activity were observed only on the outer surface of the basal plasmalemmas (fig. 3) and the basal infoldings. There was no evidence of any activity along the apical (including the microvilli) or lateral plasmalemmas or in the intracellular organelles. In control experiments, no reaction product was observed when the substrate ATP or Mg^{2+} was omitted from the incubation medium, while the presence of 10^{-3}M ouabain in the incubation medium preserved the same localization of this enzyme activity.

Both the potassium-dependent and independent p-nitrophenyl phosphatase (NPPase) were localized cytochemically to the inner surface of the plasma membrane, suggesting that their activities had similar spatial orientations with respect to the membrane (Ernst, 1972). In contrast, the Mg^{2+}-ATPase on the basal cell membrane of the choroid plexus (Torack and Barrnett, 1964; Masuzawa *et al.*, 1980) and on the salt gland (Ernst and Philpott, 1970) was localized exclusively on the outer surface of the plasmalemma. This mode of Mg^{2+}-ATPase localization does not demonstrate the internal release of hydrolyzed phosphate by ATPase, but the finding may be important in understanding the functionally unsettled Mg^{2+}-ATPase.

There is an extensive literature suggesting that much membrane-localized ATPase might be artefactual (Moses *et al.*, 1966; Rosenthal *et al.*, 1966; Moses and Rosenthal, 1967, 1968; Ganote *et al.*, 1969; Rosenthal *et al.*, 1969*a*, *b*). The lead ion present in the Wachstein-Meisel method not only inhibited the ATPase activity of fresh tissue, but was capable at pH 7.2 and 37° C of catalysing of nonenzymatic hydrolysis of ATP and it was suggested that this reaction might be a source of artefact in the lead salt method for the histochemical localization of ATPase (Rosenthal *et al.*, 1966).

When histochemical procedures for ATPase were applied to tissue, the intensity of plasma membrane staining did not correlate closely with residual tissue ATPase activity (Tormey, 1966; Moses and Rosenthal, 1967, 1968). The plasma membrane localization of reaction product was related to the magnitude of lead catalysed ATP hydrolysis, and both were functions of the concentrations of ATP and lead (Moses *et al.*, 1966; Rosenthal *et al.*, 1966). Nevertheless, although ATPase activity is partly inhibited by lead ions and there is nonenzymatic hydrolysis of ATP by lead ions,

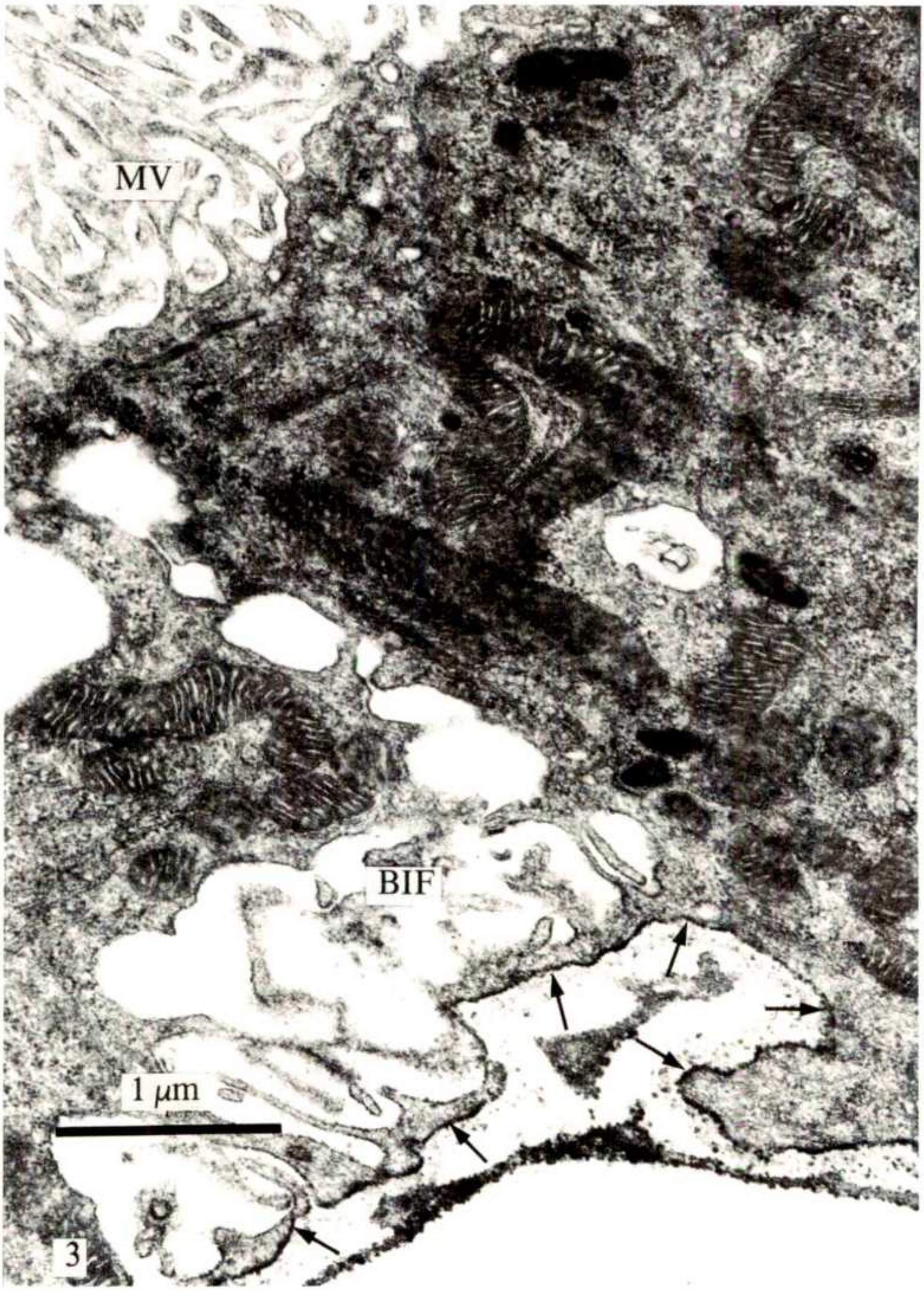


FIG. 3. Mg^{2+}-ATPase activity in rat choroid plexus epithelial cell. The plasmalemmas of the basal infoldings (BIF) show reaction products (arrows). No reaction is observable in the microvilli (MV).

some researchers have justified the Wachstein-Meisel procedure for the histochemical demonstration of ATPase (Novikoff, 1967; Jacobsen and Jørgensen, 1969; Mietkiewski *et al.*, 1970).

Novikoff (1967) documented a number of lines of evidence to support the thesis that the results obtained by the Wachstein-Meisel method were not artefact but reflected real enzymatic activity. He exposed not only heat-incubated sections but also untreated sections to forming lead phosphate as they were incubated in the Wachstein-Meisel medium in the presence of fluoride or PCBM and in the absence of enzyme inhibitors. No sign of absorption of nonenzymatically produced lead phosphate was observed. Using the modified Wachstein-Meisel medium, Jacobsen and Jørgensen (1969) challenged this problem. The staining of sections of microsomal sediments from rat kidney was compared with the *in vitro* activity of Na^+, K^+-, Mg^{2+}- and Ca^{2+}-ATPase in the presence of lead. The histochemical relevance of these observations was tested on sections of rat kidney. Localization of Na^+, K^+-ATPase was not possible at concentrations of lead below the inactivating level (0.5 mM). Mg^{2+}-ATPase and Ca^{2+}-ATPase were only partially inhibited by 3.6 mM lead and were localized to plasma membranes in glutaraldehyde-fixed kidney. In the medium used, the lead-catalysed hydrolysis of ATP contributed little to the staining of fixed kidney. From the histochemical standpoint, the inhibition of ATP hydrolysis in Wachstein-Meisel medium by cysteine is an important phenomenon. Occurring under these conditions, the histochemical reaction for the demonstration of the localization of ATPase activity was in part free from the error caused by deposition of lead phosphate, arising as a consequence of the nonenzymatic hydrolysis of ATP, in the tissues. This was most likely due to the fact that cysteine complexes Pb^{2+}, which under the circumstances, should not exert a major influence on ATP hydrolysis in Wachstein-Meisel medium (Mietkiewski *et al.*, 1970).

The role of magnesium-activated ATPase in epithelial cells. The adenosine triphosphatase activity in the nerve cell membrane is probably related to molecular transport concerned with impulse conduction and synaptic transmission (Manocha, 1970).

According to Torack and Barrnett (1964), the capillaries of brain parenchyma are particularly characterized by their limited permeability to certain electrolytes and vital dyes, this peculiarity constituting the blood-brain barrier. The capillaries in the choroid plexus and the peritubular capillaries of the kidney possess no such selective permeability and lack ATPase activity in their basement membranes. It was proposed that the distinct localization of ATPase in the basement membranes of cerebral and cerebellar capillaries is correlated with the blood-brain barrier. Shantha and Manocha (1968) thought that the presence of ATPase activity concentrated at the borders of the choroid plexus epithelial cells might be interpreted in terms of its role in providing the energy needed for the passage of CSF formed in the cell cytoplasm to the ventricle of the brain.

The magnesium-activated ATPase activity in the homogenate (without deoxycholate treatment) of lateral ventricular choroid plexus of the rabbit has been found to be high (8.3 ± 1.2 μmol Pi/mg protein/h). It was proposed that Mg^{2+}-ATPase might be involved in the formation of CSF (Miwa *et al.*, 1980).

Sodium-potassium-ATPase

Skou (1957, 1960, 1965) was the first to describe sodium-activated ATPase in the submicroscopic particles of crab nerve and subsequently this enzyme has been found in the human erythrocyte membrane (Hoffman, 1966; Post *et al.*, 1960) and in the central nervous system (Bonting *et al.*, 1961).

The connection between the activities of Na^+, K^+-ATPase and K^+-activated phosphatase, as first demonstrated biochemically by Judah *et al.* (1962), was initially proposed by Tosteson (1962). The existence of K^+-activated phosphatase, which was shown to have the ability to accelerate the hydrolysis of p-nitrophenyl phosphatase (p-NPPase) in the presence of the activating effect of K^+ requiring Mg^{2+}, has also been reported in the brain. The similarities between the Na^+, K^+-ATPase and K^+-activated phosphatase activities strongly suggest the presence of the enzymatic Na^+, K^+-dependent ATP hydrolysis system in the dephosphorylation stage of the Na^+, K^+-ATPase cycle.

Matano and Ishii (1973), using the modified incubation medium of Wachstein and Meisel (1957), observed ultracytochemically positive sites of Na^+, K^+-ATPase in the plasma membranes of the microvilli of the choroid plexus epithelial surface and also related to endoplasmic reticulum. They found that, in the presence of ouabain in the incubation medium, the intensity of the activity in the microvilli was considerably reduced while that in the endoplasmic reticulum showed only a slight change, suggesting the coexistence of Mg^{2+}-dependent ATPase activity.

Ernst (1972), employing p-nitrophenyl phosphate as a substrate and strontium as a capture ion, was able to demonstrate a correlation between osmotic stress and increased Na^+, K^+-ATPase activity in the salt gland. Ernst's technique for p-NPPase activity was previously the preferred technique. However, because of concern that Ernst's technique included the risk of producing unwanted artefacts through its two-step reaction with $Sr^{2+} + Pb^{2+}$, the one-step method of Mayahara *et al.* (1979); Mayahara and Ogawa (1980), using lead citrate as a capture reagent for the ultracytochemical demonstration of ouabain-sensitive, K^+-dependent phosphatase activity, was devised.

Masuzawa *et al.* (1981*a*) demonstrated intense electron-dense reaction products of p-NPPase activity in the plasmalemma of the microvilli and a positive reaction along the outside of the basal plasmalemmas of choroidal epithelial cells, but did not find any reaction product along the lateral and apical plasmalemmas except for the microvilli (fig. 4A, B).

Only a few reports have been available on p-NPPase activity in choroid plexus epithelial cells. To define the secretory characteristics of the choroid plexus epithelium, the Ernst technique was used by a few workers to localize Na^+,

K^+-ATPase in the frog, rabbit and rat choroid plexus (Milhorat *et al.*, 1975), in the human choroid plexus papilloma (Milhorat *et al.*, 1975) and in the choroid plexus of the adult male Wistar rat (Nakamura *et al.*, 1976). These researchers found electron-dense reaction products along the outer leaflets of the basal and lateral plasmalemma of the choroid plexus epithelial cells and in the perivascular space, but they detected no reaction product along the apical plasmalemma or along the capillary endothelium except in pinocytic pits or vesicles.

Since Milhorat *et al.* (1975) only fixed the choroid plexus for electron histochemistry with 3 per cent depolymerized paraformaldehyde for 90 min, the morphological preservation was not satisfactory for exact enzyme localization. They employed the Ernst method which includes the two-step reaction and the possible risk of unwanted artefacts.

The role of Na^+, K^+-ATPase in choroid plexus epithelial cells. Quinton *et al.* (1973) localized an ouabain-sensitive sodium pump on the apical surface of the frog choroid plexus epithelium using ^3H-ouabain autoradiography. The physiological experiment of Wright (1972*a*) indicated that Na^+ was secreted into the CSF across the apical plasmalemma (brush border) by an ouabain-sensitive sodium potassium exchange pump. Masuzawa *et al.* (1981*a*), from the results of their ultracytochemical localization of p-NPPase activity, suggested that Na^+ entered the choroid epithelial cells from the basal plasmalemma by means of a Na^+ pump facing the capillary endothelium, that the incorporated Na^+ was transferred to the microvilli area by diffusion, and that it was then secreted into the CSF through the Na^+ pump existing in the microvilli.

It is generally accepted that the choroid plexus plays a major role in the production and regulation of CSF and recently evidence has accumulated confirming that CSF is formed largely by active secretion rather than merely by ultrafiltration or dialysis of plasma (Fishman, 1959; DeRougemont *et al.*, 1960; Becker, 1961; Welch, 1962; Vates *et al.*, 1964; Wright, 1972*b*). The active transport of Na^+ across the choroid plexus has long been implicated as the driving force behind CSF secretion. According to Wright's model (Wright, 1972*a*), which accounts for ion transport across choroidal epithelial cells, Na^+ was shown to provide the electrochemical gradient for uphill transport of this solute, and to be secreted into the CSF across the brush border by an ouabain-sensitive Na^+, K^+-exchange pump. The active fluxes of Na^+ and K^+ at the apical surface were shown to be coupled, as an ouabain-sensitive pump (Na^+, K^+-ATPase). The possibility that coupled Na^+ and hydrogen fluxes took place at the serosal face in the epithelial cells was also considered.

Glucose-6-phosphatase (E.C.3.1.3.9)

The glucose-6-phosphatase (G6Pase) which hydrolyses glucose-6-phosphate has been found in a variety of mammalian tissues. This enzyme is present in the endoplasmic reticulum and is commonly used as a marker enzyme. It is absent from

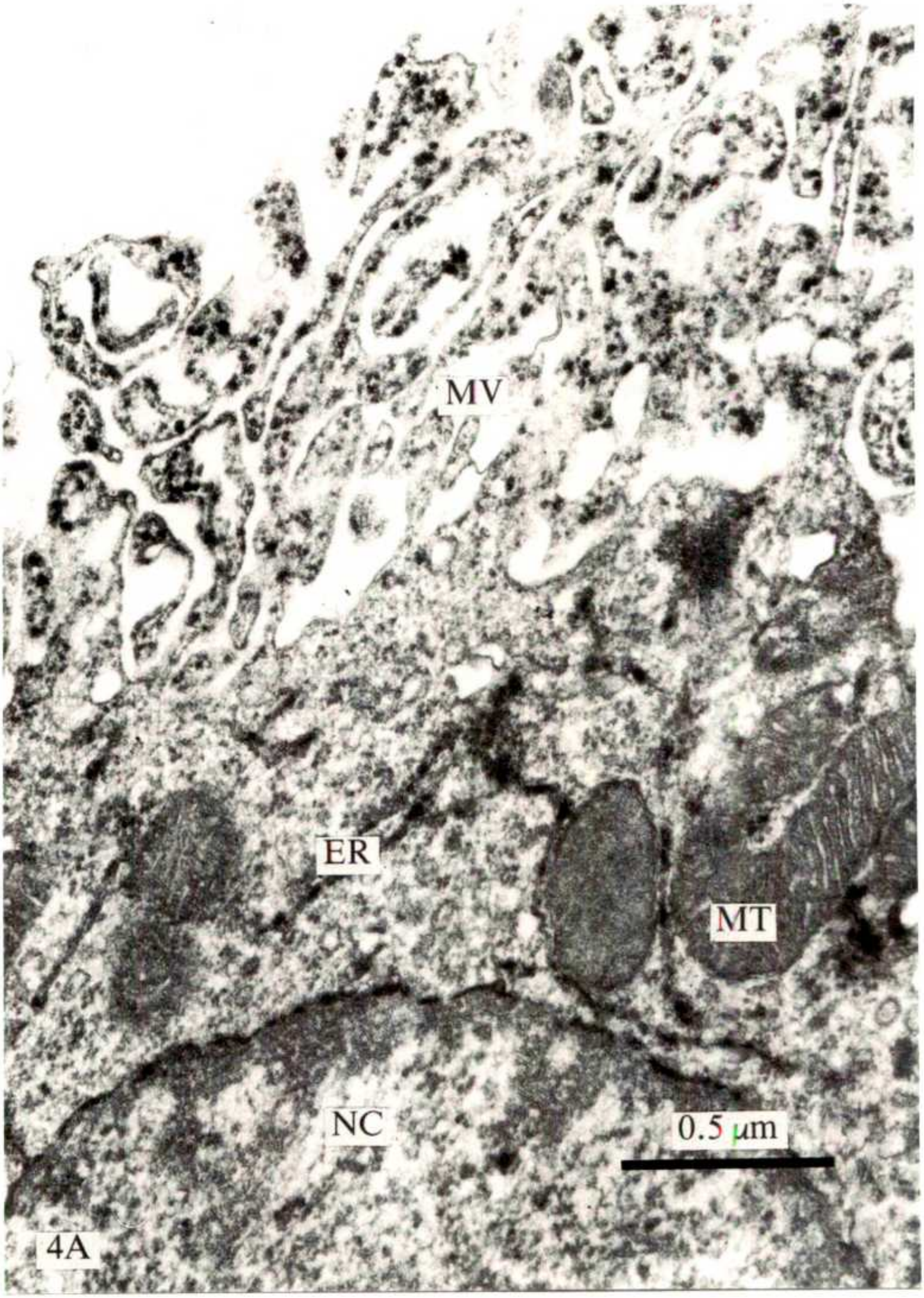
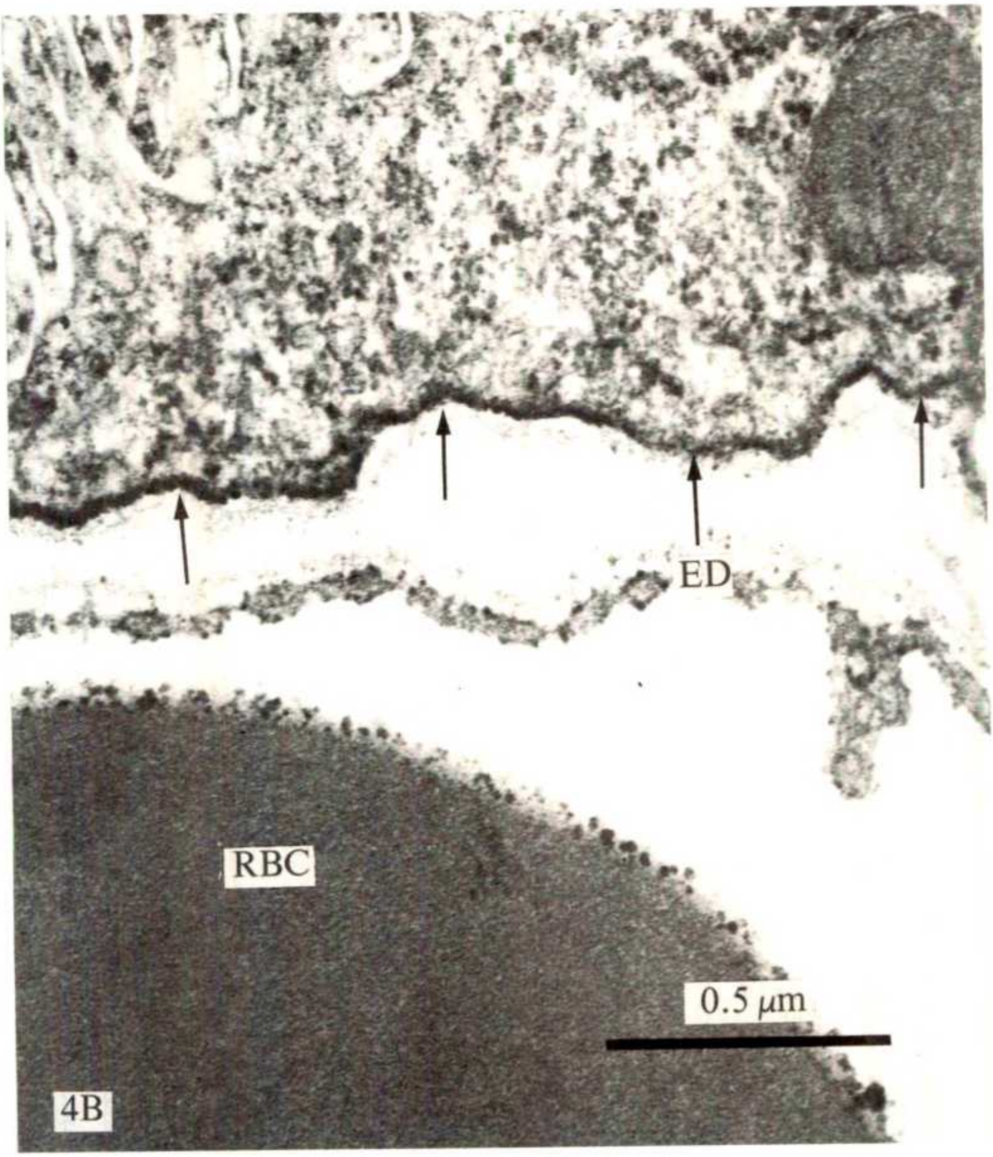


FIG. 4. p-Nitrophenylphosphatase activity in rat choroid plexus epithelial cell. A, the reaction products are localized in the microvilli (MV). The endoplasmic reticulum (ER) and the membrane of the nucleus (NC) show some reaction deposits. MT = mitochondria. B, the reaction products are found along the outer leaflets of basal plasmalemma (arrows), in the capillary endothelial cell (ED) and on the surface of a red blood corpuscle (RBC).

the liver in cases of glycogen storage disease, but is otherwise present in all mammalian organs capable of releasing glucose into the blood stream.

Using light microscopy to study G6Pase activity in the choroid plexus, Shantha and Manocha (1968) observed that it was concentrated in the nucleoli of the lining cells which gave a strong reaction, in the nucleus of the cytoplasm which gave a moderate reaction and in the stroma which showed mild activity. On the other hand, the fine structure of G6Pase localization in this tissue has not been established. Tice and Barrnett (1962*b*) first reported the ultracytochemical localization of



G6Pase activity in rat liver cells, where it was found in both the smooth and the rough endoplasmic reticulum and in the nuclear envelope.

In spinal ganglion cells, the nucleolus was positive for glucose-6-phosphatase in some cells, whereas in others the whole nucleus was positive (Tewari and Sood, 1969). It was considered that these results represented a real variation in the distribution of enzyme activity and were not artefactual. It was suggested that the nucleolus may synthesize ATPase and G6Pase and pass it on to the cytoplasm.

Glucose-6-phosphatase, which is generally considered to be a marker enzyme for endoplasmic reticulum, was found in the fractions for microsomes, nuclear membranes and nuclei in the rat liver. The ratio of the activity was 0.05 for nuclear membrane/nuclei and 0.014 for nuclear membrane/microsomes (Franke *et al.*, 1970). In the choroid plexus epithelial cells of the rat, Masuzawa *et al.* (1980), using the Wachstein-Meisel method (1956), observed electron-dense deposits only in cytoplasmic organelles such as the endoplasmic reticulum, the nuclear envelope between the outer and the inner nuclear membrane and the trasitional elements near the Golgi complex (fig. 5). No reaction product was observed in the nucleus.

The role of G6Pase in choroid plexus epithelial cells. The localization of G6Pase activity in the choroid plexus epithelial cells was fundamentally identical to that in rat liver cells (Saito and Ogawa, 1967). G6Pase was also a good marker enzyme for the choroidal epithelial endoplasmic reticulum. The localization of G6Pase in the epithelial cells indicated that the final step of glycogenesis, the formation of glucose from glucose-6-phosphate, was being carried out in the cisternae of the endoplasmic reticulum, not in the cytoplasmic matrix.

Thiamine Pyrophosphatase

Novikoff and Goldfischer (1961) found that the thiamine pyrophosphatase (TPPase) technique acts specificially as a marker enzyme for the Golgi complex.

In the choroid plexus epithelium, the localization of TPPase activity has been studied mainly by light microscopy. Cancilla *et al.* (1966) studied the histochemistry of TPPase in the developing rat choroid plexus by the modified Gomori technique (Becker *et al.*, 1960). They found that choroidal cell activity was limited in fetal rats to a few discrete perinuclear rods and spheres, measuring 0.1 to 0.8 μm at the largest. By the seventh day the activity sites took on a more rod-like and lamellated form, recognizable as the Golgi lamellae of the adult choroid cell. In fetal rats, minimal enzyme activity barely outlined the blood vessels. Within the first week there was a marked increase in blood vessel activity up to the adult level.

Bartoníček and Lojda (1964), using the Novikoff and Goldfischer technique (1961), demonstrated the distribution of TPPase activity in the choroid plexus of four animal species and observed different localizations of this enzyme. The epithelia of the rat, mouse, guinea pig and golden hamster revealed no enzyme activity. Except for the rat, the endothelia showed no activity in these four species, whereas, apart from the golden hamster, the basement membranes of the four

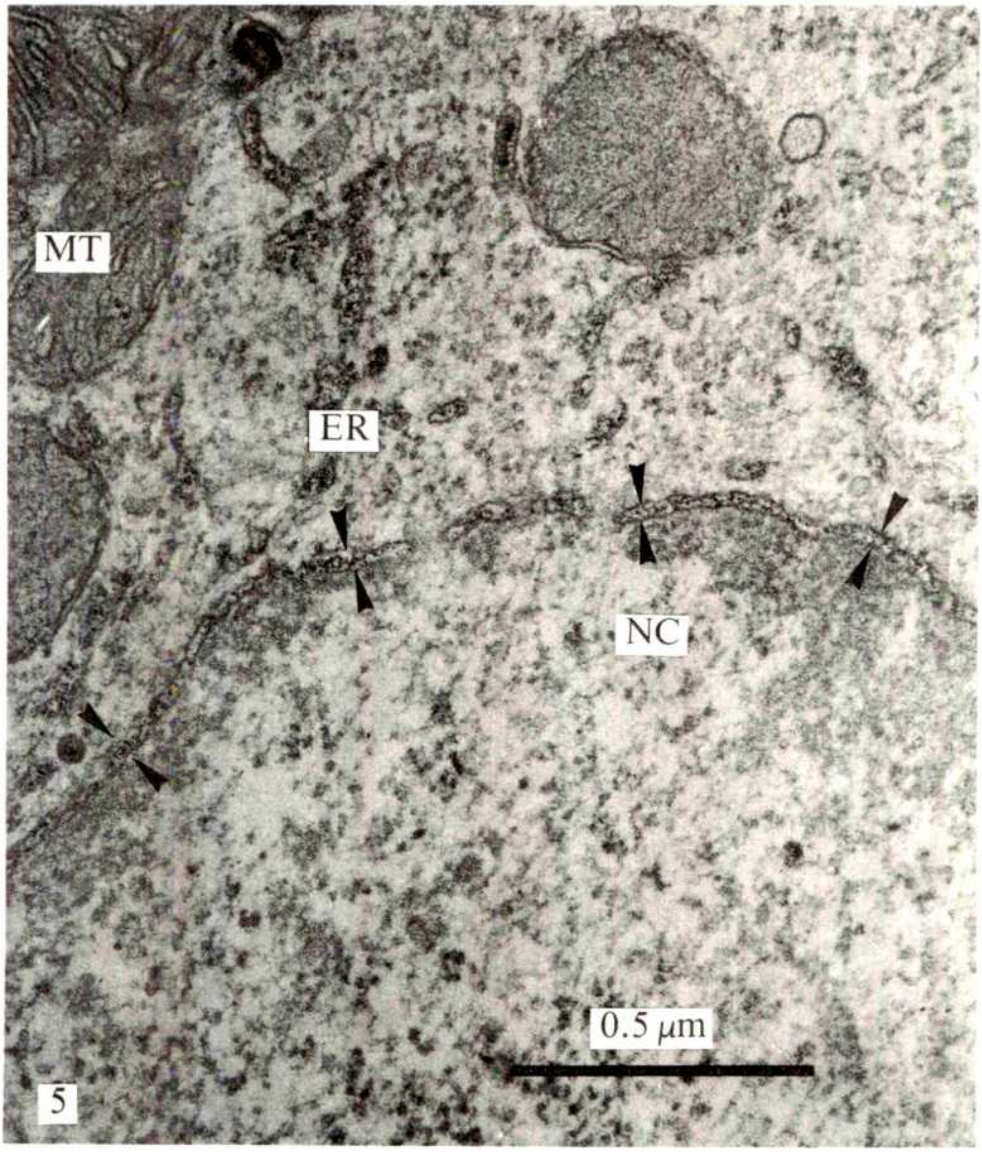


FIG. 5. Glucose-6-phosphatase activity in rat choroid plexus epithelial cell. The rough endoplasmic reticulum (ER) and the space between the inner and outer membranes of the nucleus (NC) show the reaction products (arrow heads). The mitochondria (MT) are devoid of deposits.

species showed activity. Shantha and Manocha (1968) also employed the Novikoff and Goldfischer technique and found TPPase activity in the choroid plexus epithelium of the monkey. The lining cells of the choroid plexus showed well-developed Golgi complexes distributed throughout the cytoplasm. They noted that the form of the Golgi complex varied at different cells. Some cells contained darkly stained, highly fenestrated networks, whereas others showed a lightly stained

TPPase positive Golgi complex. The nucleoli of all these cells showed mild diffuse TPPase activity. The nucleus was negative. The cytoplasm between the stained Golgi materials was clear and unstained. The stromal vessels showed a diffuse type of strongly positive TPPase activity.

Masuzawa *et al.* (1981*c*), using the Novikoff and Goldfischer technique, described the ultracytochemical localization of TPPase activity in the choroid plexus epithelial cells of the rat. The most distinct finding in the epithelial cells was the fact that the Golgi complex located near the nucleus showed electron-dense reaction product related to TPPase activity. Reaction products of lead phosphate were observed in the cisternae of the Golgi complex, where the reaction was usually restricted to the two or three inner lamellae of the Golgi cisternae (fig. 6). The endoplasmic reticulum and the nuclear envelope showed no enzymatic activity. No deposit was observed

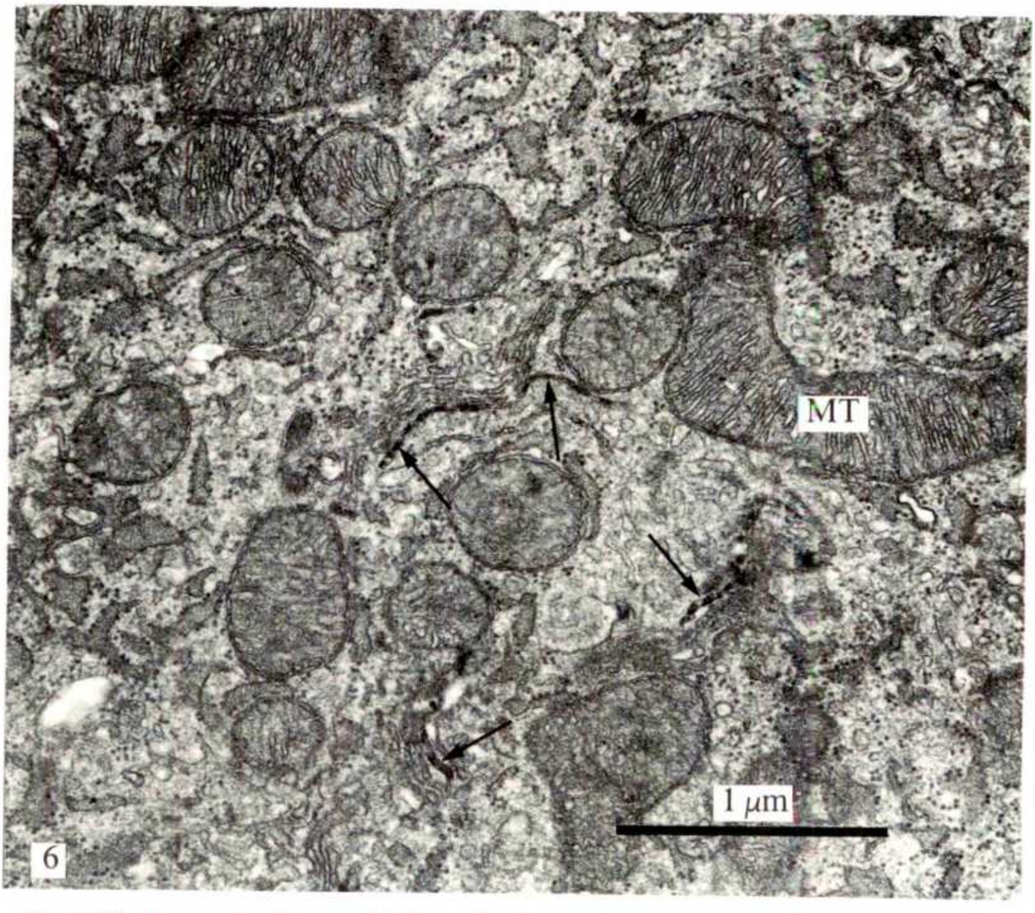


FIG. 6. Thiamine pyrophosphatase activity in rat choroid plexus epithelial cell. The lamellae of Golgi cisternae (arrows) show the electron-dense reaction products. The mitochondria (MT) and the other organelles are devoid of reaction products.

in the other intracellular organelles such as lysosomes, mitochondria, nucleus or vesicles, neither were any reaction products present in the apical, lateral or basal plasmalemma. In these it was accepted that TPPase, for epithelial cells as well as liver cells, is a marker enzyme for the Golgi complex (Novikoff and Goldfischer, 1961; Saito and Ogawa, 1966). According to Shantha and Manocha (1968), the fact that the morphology of the TPPase-positive Golgi complex of the choroid plexus was so fundamentally different from that of the ependymal cells, in spite of their similar origin, was of particular interest.

The role of TPPase in choroid plexus epithelial cells. Shantha and Manocha (1968) noted that the choroid plexus epithelial cells contained large quantities of reticular Golgi networks of various types, suggesting secretory activity. They considered that it might be worth examining the effect of vitamin B_1 on the morphology of the Golgi complex in the choroid plexus epithelial cells. It has been assumed that the localization of TPPase activity in the innermost lamellae of the Golgi complex reflected the existence of functional difference in the Golgi complex (Saito and Ogawa, 1966).

Adenylate Cyclase (E.C.4.6.1.1)

The reaction of adenylate cyclase (AC) can schematically be represented as follows:

$$\text{ATP} \xrightarrow{\text{AC}} 3^1:5^1\text{-cyclic AMP} + \text{pyrophosphate (PPi)}$$

Attempts to demonstrate AC activity are fairly recent. A method was proposed by Reik *et al.* (1970), but Lemay and Jarett (1975) objected that what had been demonstrated was not enzyme activity, but artefact, as the presence of 3×10^{-3} M lead nitrate in the incubation medium completely inhibited enzyme activity. Although several attempts have been made to avoid enzymatic inhibition by heavy metals, for example, by using a barium salt (Kempen *et al.*, 1978) or calcium (Rechardt and Hervonen, 1976; Rechardt and Härkönen, 1977), the electron-dense deposits due to AC activity have not been satisfactorily demonstrated.

The histochemistry of AC in brain tissue has not been satisfactorily developed because of this dilemma. Rechardt and Härkönen (1977) demonstrated alloxan-sensitive and dopamine-stimulated AC activity in the plasma membrane and the postsynaptic membrane of the rat caudate nucleus, and noradrenaline-stimulated AC activity in postsynaptic membranes in the rat cerebral cortex. Another trial was performed by Krstić (1977) in the rat and in the pineal body of the mongolian gerbil.

The authors employed the incubation medium devised by Araki and Saito (1979), a modification of that of Howell and Whitfield (1972) which used AMP-PNP as a substrate and lead citrate (1.3×10^{-3} M) for the capture reagent. Electron microscopy was employed to detect AC activity in the rat choroid plexus and ventricular ependymal epithelial cells. Reaction products were observed in the choroidal

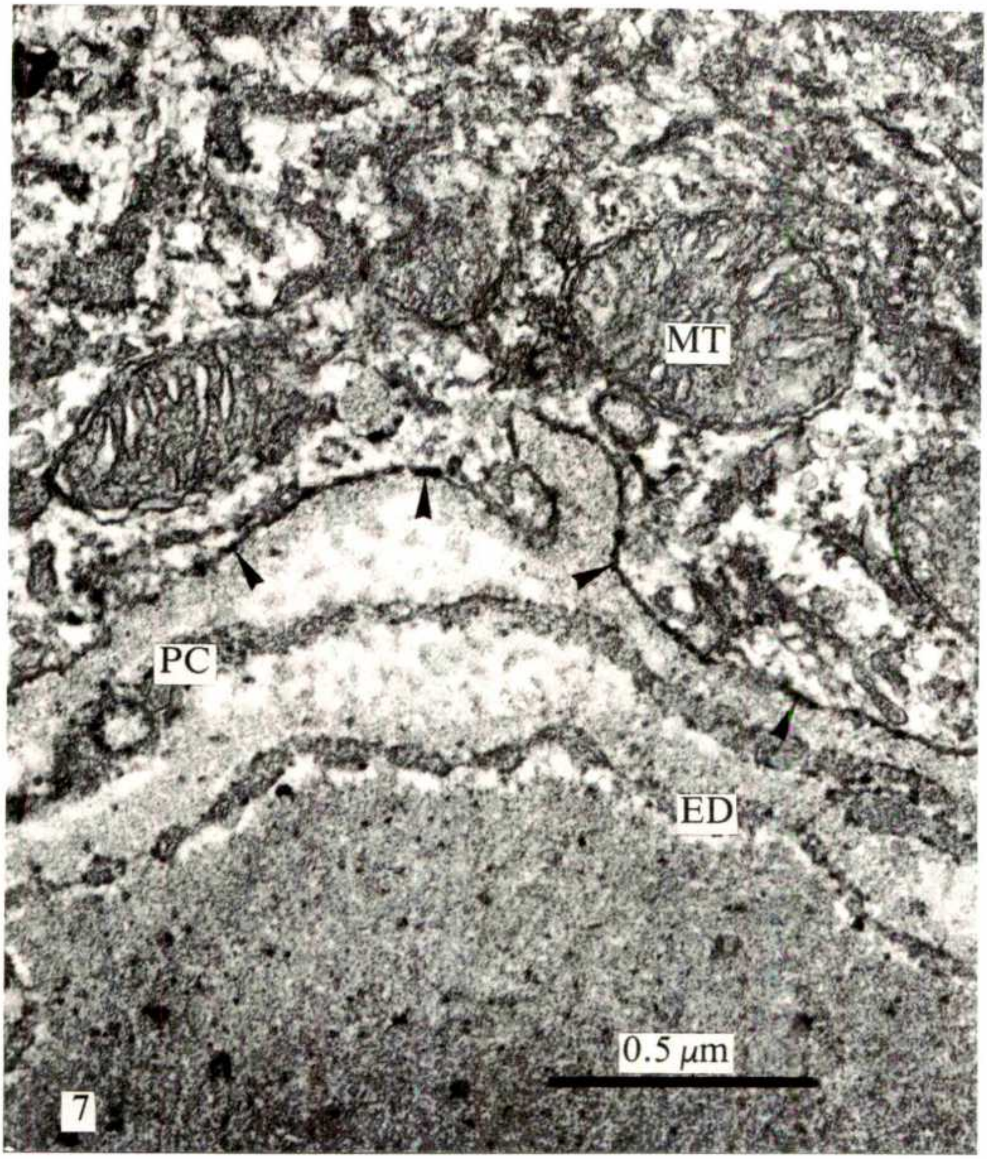


FIG. 7. Adenylate cyclase activity in rat choroid plexus epithelial cell. The electron-dense reaction products are prominent along the basal plasmalemma (arrow heads). Some questionable deposits are seen in a pericyte (PC) and the capillary endothelial cell (ED). MT = mitochondria.

epithelial cells along the basal plasmalemma but were less noticeable in the endothelial cells (fig. 7) which were inhibited by 5×10^{-3}M alloxan.

The reaction was negative along the apical and lateral plasmalemmas and in the cytoplasm, including the intracellular organelles. In the ventricular epithelial cells, the reaction products were observed along the apical plasmalemmas including the surface of microvilli and cilia. In control experiments, 5×10^{-3} M alloxan in the incubation medium effectively inhibited enzyme activity in the ventricular epithelial cells (Masuzawa *et al.*, 1981*a*).

The role of adenylate cyclase in choroid plexus epithelial cells. Epstein *et al.* (1977) documented increased CSF secretion through stimulation of AC-cyclic AMP by the intraventricular administration of cholera toxin. AC-cyclic AMP may therefore be implicated as a mediator in the control of ventricular fluid production. Nathanson (1979) obtained biochemical evidence supporting the hypothesis of sympathetic control of CSF production by the identification of a specific β-adrenergic sensitive AC in the choroid plexus.

Our observation of AC activity, inhibited by alloxan, in the rat choroidal and ventricular epithelium was noteworthy as this enzyme had hardly been examined before at the ultracytochemical level.

Carbonic Anhydrase

Carbonic anhydrase (E.C.4.2.1.1) (CAHase) was first demonstrated in blood cells of the rat by Meldrum and Roughton (1933). This enzyme was shown to act as a catalyst for the reversible reaction $CO_2 + H_2O \rightleftarrows H_2CO_3$. In nervous tissue, CAHase was first demonstrated biochemically by van Goor (1940) and subsequently studied in detail by Ashby (1944*a*, *b*). The more accurate localization and activity of this enzyme in the brain was studied by microanalyses of different cells of CNS: nerve cells, glia and choroid plexus epithelial cells (Giacobini, 1961, 1962). It is now well established that CAHase is present in large amounts in the choroid plexus epithelium (Maren, 1967) and that the CSF secretion is reduced after inhibition of this enzyme by acetazolamide, a specific inhibitor for this enzyme. The activity of CAHase in the choroid plexus has been studied biochemically by Fisher and Copenhaver (1959) and Giacobini (1961).

By the use of histochemical methods, the localization of CAHase activity has been investigated in other secretory epithelia and in epithelia engaged in electrolyte transport (Häusler, 1958; Korhonen *et al.*, 1964; Korhonen and Korhonen, 1965; Korhonen *et al.*, 1966; Leder, 1966; Hansson, 1968; Hyppä, 1968; Winborn *et al.*, 1974; Roussel *et al.*, 1979). The localization of CAHase in the choroid plexus epithelium has been studied by a few researchers at the light microscopic level (Korhonen *et al.*, 1964; Roussel *et al.*, 1979). Korhonen *et al.* (1964), using the incubation medium of Häusler (1958), observed that a very intense positive reaction, which was only a little fainter than the reaction of erythrocytes, was obtained in the most external layer of the mouse choroid plexus epithelium. Roussel *et al.* (1979) studied the localization of carbonic anhydrase C isoenzyme in the CNS of the rat employing the indirect immunoperoxidase technique and found no activity in the ependymal cells of the lateral ventricle, but observed intensely positive activity in the choroid plexus epithelium.

Masuzawa *et al.* (1981*d*) studied the localization of CAHase activity in the rat choroid plexus epithelial cells by electron microscopy using a modification of Hansson's method (Yokota, 1969). Numerous electron-dense reaction products were found in the microvilli of the choroidal epithelial cells (fig. 8A). The reaction deposits were also particularly evident in the infoldings of the basal plasmalemma (fig. 8B), but to a lesser extent in the microvilli. The localization was mainly on the plasma membrane, but some reaction products were also noted in the cytoplasm near the plasmalemma. Hardly any reaction products were observed in the intracellular organelles except for occasional deposits in mitochondria. Carbonic anhydrase activity was inhibited by 10^{-3} M acetazolamide in the incubation medium.

The role of carbonic anhydrase in the choroid plexus. The localization of CAHase in brain mitochondria reported by Karler and Woodbury (1960) was explained by the fact that the rat cerebral cortex displays enzymatic activity both in the particulate and soluble fractions (soluble fraction, 75 per cent of the total enzyme activity; mitochondrial fraction, 20 per cent; nuclear fraction, 5 per cent). They concluded that CAHase in the brain was bound to the mitochondrial membranes.

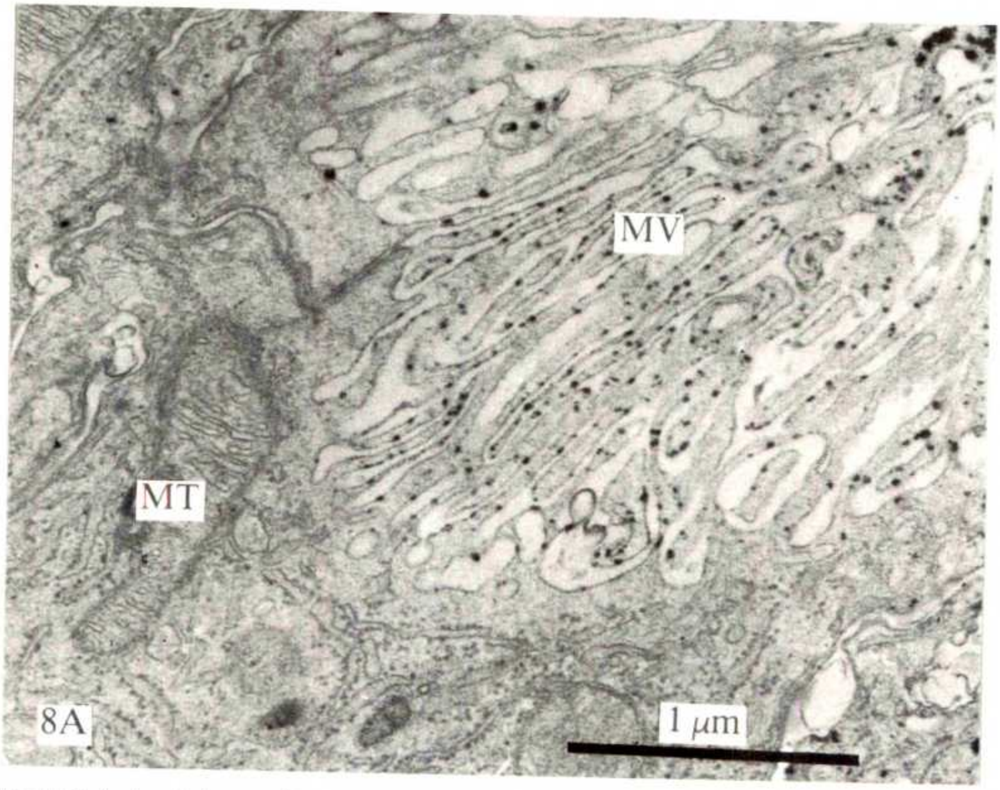


FIG. 8. Carbonic anhydrase activity in rat choroid plexus epithelial cell. A, the electron-dense reaction products are found in the microvilli (MV). MT = mitochondria. B, the reaction products are also seen in the basal infoldings (BIF) of the epithelial cell. MT = mitochondria.

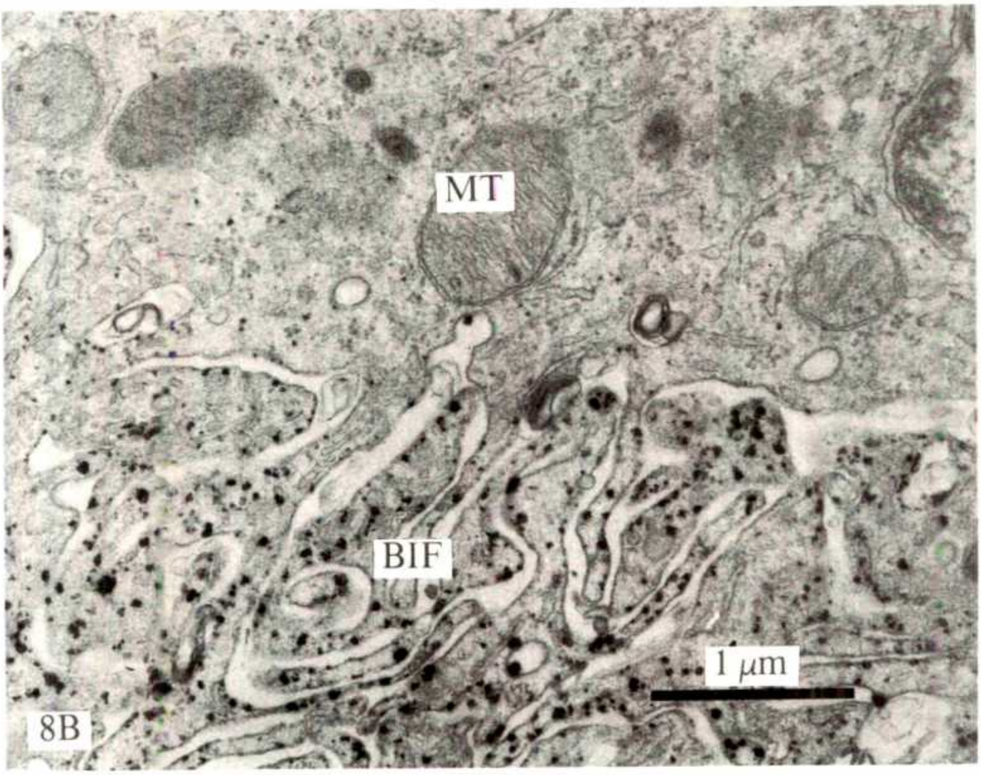
As a result of the cytochemical study of liver cells in the mouse, Yokota (1969) supported their conclusion in terms of the electron-dense deposits which were observed on the external membranes of the mitochondria.

The immunohistochemical localization of CAHase C isoenzyme activity in the rat brain at the electron microscopical level by Roussel *et al.* (1979) indicated that specific localization was found in the cytoplasm of glial cells in the absence of the staining of such cytoplasmic organelles as mitochondria and nuclei. Their findings also confirmed the report of Yandrasitz *et al.* (1976) who found no CAHase activity either in the membranes or matrices of the mitochondria and very low CAHase C isoenzyme activity in the microsomal fraction.

Carbonic anhydrase, which was found in high concentration in the choroid plexus (Maren, 1967; Fisher and Copenhaver, 1959), is likely to be connected with the active transport process as well as Na$^+$, K$^+$-ATPase (Masuzawa *et al.*, 1981*a*).

Oxidoreductase

Kaluza *et al.* (1964), studying the localization of oxidoreductase activity in the chick choroid plexus at various stages, found that moderate activity of cytochrome oxidase (CYO) was present in the 9-day-old chick (36th stage) plexus, but the activity increased only slightly with age, showing activity in epithelial cells with an



enhanced staining of the brush borders. Diphospho- and triphosphopyridine nucleotide tetrazolium reductase showed marked activity in the epithelial cells of the choroid plexus with increasing age. They also demonstrated succinic dehydrogenase (SDH) activity in the choroid plexus epithelium. This enzymatic activity was essentially the same as that of CYO in that the dye was primarily localized in the brush border and was less on the inner portion of the cell and inner wall. The dehydrogenases of the Embden-Meyerhof glycolytic pathway, glyceraldehyde-3-phosphate dehydrogenase, glucose-6-phosphate-dehydrogenase and β-hydroxybutyrate dehydrogenase displayed very little or no activity until the 21st day in the chick embryo (stage 46), but lactic dehydrogenase (LDH) showed high activity in the inner wall and brush borders of the epithelial cells.

In the developing rat choroid plexus, Cancilla *et al.* (1966) observed minimal cytoplasmic LDH activity which was followed by a progressive increase to a maximum in the weanling and the adult rat choroid plexus epithelium.

From the histochemistry of the choroid plexus in the rat and monkey, Shantha and Manocha (1968) described strong LDH and NADH dehydrogenase (DPN diaphorase) activity in the cytoplasm of epithelial cells which showed as both diffuse and granular deposits; moderately strong glucose-6-phosphate dehydrogenase (G6PDase) activity in the cytoplasm; fairly strong SDH and CYO activity in the cytoplasm of both diffuse and granular appearance; and moderately strong monoamine oxidase (MAO) activity both in the cytoplasm and the nuclei of the rat choroid plexus, but only in the cytoplasm of the monkey. Shimizu *et al.* (1959) demonstrated by light microscopy that the choroid plexus as well as the ependymal cells were weakly positive for MAO activity in rodents. On the other hand, Arioka and Tanimukai (1957) observed, in the same tissues, an intense positive reaction for MAO activity, as they also did in the capillary walls of the adult mouse.

Leduc and Wislocki (1952) studied SDH activity in rat choroid plexus epithelia and observed that this tissue was as reactive as the cerebral and cerebellar grey matter, exhibiting a moderate red background plus a fairly dense accumulation of medium-sized blue cytoplasmic granules. Becker *et al.* (1960) demonstrated heavily stained DPNH- and TPNH-tetrazolium reductase activity in the epithelia of the ependyma and the choroid plexus of the rat.

Esterase

Leduc and Wislocki (1952) found that the greatest activity of nonspecific esterase was detectable as a dense intracellular particulate aggregate of red dye in the epithelium of the rat choroid plexus using the method of Nachlas and Seligman (1949). Bartoníček and Lojda (1964), using the method of Davis and Ornstein (1959) for the detection of nonspecific esterase, demonstrated very high activity in the epithelium of the choroid plexus of the rat, guinea pig and golden hamster, and surprisingly low activity in that of the mouse.

In the rat choroid plexus, Shantha and Manocha (1968) recorded simple esterase activity in the lining cell cytoplasm and in the nuclei and a negative reaction of specific cholinesterase (AChE) and of nonspecific cholinesterase (BChE) in the choroid plexus epithelium by using the technique of Coupland and Holmes (1957). Joó and Csillik (1966), using Koelle's technique (1954), observed well-defined butyrylcholinesterase in capillaries throughout the CNS. However, those in CNS areas that were located outside the blood-brain barrier, for example those of the choroid plexus, the pineal gland, the pituitary gland and the area postrema, were devoid of this enzyme activity. Fishman and Hayashi (1962) also noticed mild activity of indoxyl esterase in the surface epithelia of the rat choroid plexus.

Several Hydrolases

Cancilla *et al.* (1966), using a modified technique (Becker *et al.*, 1960), found no activity of adenosine diphosphatase or 5′-nucleotidase in the blood vessels of the developing rat choroid plexus until the first week after birth, after which activity was maintained into the adult phase. At no time was cytoplasmic activity noted.

Considerable species differences have been reported for various nucleotide phosphatase activities in the choroid plexuses of the rat, mouse, guinea pig and golden hamster (Bartoníček and Lojda, 1964). In the endothelium of the choroid plexus, splitting of adenosine monophosphate, diphosphate and triphosphate was recorded only in the rat and the positive reaction was observed when one of these substrates was used. Bartoníček and Lojda (1964), using the method of Nachlas *et al.* (1956), detected aminopeptidase activity solely in fibrocytes lying under the choroidal epithelium of the guinea pig.

In studies on the histochemistry of β-glucuronidase activity, Kroh and Renkawek (1973) obtained moderate activity in the mouse choroid plexus. Finally, Davidoff and Galabov (1976), using the modified method of Hayashi (1965) and Gossrau (1972, 1973), demonstrated in the rat choroid plexus epithelium, strong activity in the pericytes surrounding the capillaries and strong N-acetyl-β-D-glucosaminidase activity mainly in the apical part of the epithelium.

Other Enzymes

In the developing rodent choroid plexus, Shimizu and Okada (1957); employing the technique of Goldberg *et al.* (1952) and of Takeuchi and Kuriaki (1955), examined the localization of phosphorylase activity. A slight purplish brown staining was encountered directly after birth. Very intense activity in the epithelium was observed from 3 to 10 days of age, evident as deeply coloured granules attached to the epithelial surface and as diffuse staining of the epithelium. Enzyme activity began to decline from 14 days of age and a slight reaction or no reaction at all was detectable between one month and maturity.

Albert *et al.* (1966) showed a very intense histochemical reaction for γ-glutamyl transpeptidase activity in the epithelium which covered the leaves and the villi of the choroid plexus in the rabbit. This activity was much less prominent in the choroid plexus of man and other mammals. While some enzymatic activity was exhibited by the capillaries of this tissue in man, none could be seen in other mammals.

In the choroid plexus of the squirrel monkey, Shantha and Manocha (1968) observed moderate aldolase activity in the lining cells of the choroid plexus and a negligible reaction in the stroma. It was interesting that in aldolase preparations there were a large number of mast cells giving a strongly positive reaction for this enzyme. Their granules were especially noticeable in the choroid plexus of the fourth ventricle.

CEREBROSPINAL FLUID FORMATION AND ACTIVE TRANSPORT IN THE CHOROID PLEXUS

The largest part of CSF formation takes place in the choroid plexuses. As already emphasized, CSF formation is an active secretion (DeRougemont *et al.*, 1960; Ames *et al.*, 1964, 1965*a*, *b*; Holloway and Cassin, 1972) and, for these active transport processes, metabolic energy is necessary. Carbonic anhydrase and Na^+, K^+-ATPase activity can be demonstrated biochemically in the choroid plexus and the importance of this for the CSF secretory function has been studied after enzyme inhibition by specific inhibitors. Both CAHase and Na^+, K^+-ATPase have been shown to be metabolically essential for CSF secretion (Tschirgi *et al.*, 1954; Vates *et al.*, 1964; Smith *et al.*, 1974; Masuzawa *et al.*, 1981*a*). Inhibition of these two enzymes dramatically alters CSF secretion. The specific inhibitors are ouabain for Na^+, K^+-ATPase and acetazolamide for CAHase.

Welch (1963) described the inhibitory effect upon the relative rate of production of CSF for several inhibitors and concluded that of these, acetazolamide was effective both intravascularly and topically, cardiac glycosides were effective topically but not when given intravenously, and cyanide and 2,4-dinitrophenol were ineffective topically. According to Vates *et al.* (1964), ouabain when introduced intraventricularly causes inhibition of CSF flow, which is complete at a 10^{-5} M concentration and absent at 5×10^{-10}M, whereas it is virtually inactive when administered intravascularly. It was concluded that the choroid plexus Na^+, K^+-ATPase system has a primary function in the formation of CSF, presumably through the active secretion of Na^+ into the ventricle by the Na^+, K^+-ATPase system which would have to be located on the ventricular side of the choroid plexus epithelial cells. When applied topically to the plexus, acetazolamide did not affect CSF electrolyte composition, but ouabain caused a 55 per cent increase in the CSF K^+ concentration. Smith *et al.* (1974) noted that intravenous acetazolamide reduced CSF production by 75 per cent and intraventricular ouabain produced a 71 per cent reduction. A combination of intravenous acetazolamide and intraventricular ouabain resulted in a 95 per cent reduction in CSF production.

Tschirgi *et al.* (1954) suggested that normally CAHase accelerates the formation of H^+ and HCO_3^- from CNS CO_2 within the blood-brain barrier. These ions are exchanged for plasma anions and cations, largely Na^+ and Cl^-, which thus enter the interstitial fluid of the CNS. By virtue of the relative impermeability of the blood-brain barrier to electrolytes, water enters from the plasma to maintain osmotic equilibrium. This mechanism is considered to exist not only in the choroid plexus but throughout the CNS parenchymal vasculature. Acetazolamide thus diminishes the rate of formation of both the CNS interstitial fluid and CSF.

The fact that acetazolamide alters the formation and electrolyte composition of CSF by decreasing the active transport of Cl^- in the CSF shows the relationship between this enzyme and CSF production (Maren and Robinson, 1960; Hogben *et al.*, 1960). Evidence has been offered to support the idea that the apical membrane of the epithelial cells of the choroid plexus that faces the CSF is one such site of Na^+, K^+-transport (Ames *et al.*, 1965*a*; Bradbury and Štulcová, 1970; Wright, 1972*a*; Quinton *et al.*, 1973; Johanson *et al.*, 1974). Quinton *et al.* (1973) demonstrated that an ouabain-sensitive sodium-potassium exchange pump which is linked to the activity of membrane-bound Na^+, K^+-ATPase, resides on the apical surface of the choroid plexus epithelial cells. They observed by autoradiography that ^3H-ouabain is bound to the apical membrane of the choroid plexus epithelium and detected localized ouabain-sensitive Na^+, K^+-ATPase only in the membrane facing the CSF.

The existence of a water transport mechanism for the formation of CSF against an adverse osmotic gradient was demonstrated experimentally by Heisey *et al.* (1962), Curl and Pollay (1968) and Pollay (1975). Pollay (1975) applied the Diamond and Bossert principles for the standing gradient hypothesis (Diamond and Bossert, 1967) to the choroidal ependyma. In his proposed model, the first step in the formation of CSF would be the movement of an ultrafiltrate of blood plasma through the fenestrated capillaries under the influence of a hydrostatic gradient. After the large particles have been filtered out by the basement membrane and stroma, the filtrate would then enter the basal infoldings of the choroidal cells (backward channels). As the filtrate enters these channels it is isotonic to blood. With the active transport of sodium into the cells, the fluid in the channel becomes hypotonic as it approaches the blind end of the channel, thus establishing an osmotic gradient favourable for water flow into the cells. A similar process occurring within the intercellular cleft (between adjacent choroidal cells but proximal to the tight junctions) is quite possible. The second place where water and the major transported ion interface would be the apical surface of the choroidal cells, which are also highly convoluted with microvilli. A similar mechanism would then operate to couple solute and solvent movement into the ventricular system *via* the forward (microvilli) channels. As with the apical interface, the basic process requires the expenditure of energy for transapical solute (sodium) movement.

Another hypothetical model for CSF formation was introduced by Woodbury (1971). This model postulates that the secretion of CSF is due to a Na^+, K^+-exchange pump in the membranes of the choroid plexus facing the CSF, that these membranes are highly permeable to K^+, Cl^- and HCO_3^- and impermeable to Na^+, and that the membranes facing the blood have no pump, a high permeability to K^+, Cl^-, HCO_3^- and a lesser, but still large, permeability to Na^+.

Wright (1972*a*) also advanced a model to account for ion transport across the choroidal epithelium. Sodium enters the basal surfaces of the epithelial cells from the plasma filtrate down an electrochemical gradient and is secreted into the CSF across the apical surface by an ouabain-sensitive sodium potassium exchange pump. It is assumed that sodium and hydrogen fluxes at the basal face of the cells are coupled in some fashion and that the basal face of the cells is less permeable to bicarbonate than the apical face, the reverse being true for potassium.

Rapoport (1975) presented the most satisfactory current model for ion and water transport at the choroid plexus, as extrapolated from the models by Woodbury (1971) and Wright (1972*b*). In this model, the Na^+, K^+ pump is placed at the apical villous surface of the choroidal epithelium and drives Na^+ into the CSF and K^+ into the cell. Na^+ transport into the CSF is optimized if it is accompanied by HCO_3^- and Cl^- movement in the opposite direction. Bicarbonate ion and H^+ are formed within the cell from CO_2 and water, catalysed by CAHase. Water secretion arises from standing osmotic gradients set up by a Na^+ pump at either the apical microvilli or within the lateral intercellular spaces.

The authors (Masuzawa *et al.*, 1981*a*) studied ultracytochemically the localization in the choroid plexus of K^+-dependent p-nitrophenylphosphatase (K^+-dependent p-NPPase) activity inhibition by ouabain. This reflects the potassium-stimulated dephosphorylation step of the Na^+, K^+-ATPase reaction sequence. Sites of K^+-dependent p-NPPase activity were observed in the microvilli or along the inner leaflets of the microvilli, which is in good agreement with Quinton *et al.* (1973). Along the outer leaflets (extracellular side) of the basal plasmalemmas, fewer sites were observed than in the microvilli. These findings revealed the difference in ultracytochemical localization of K^+-dependent p-NPPase activity on the epithelial cell membrane between the microvilli, where reaction products were observed inside the plasma membrane, and the basal plasmalemma, where precipitation was observed on the outer side of the plasma membrane. It might be possible to suggest that Na^+ enters the choroidal epithelial cells from the basal plasmalemma under a Na^+ pump facing the stroma, that the incorporated Na^+ is transferred to the microvilli by diffusion and that it is then secreted into the CSF through the Na^+ pump existent in the microvilli. This interpretation, using the Diamond-Bossert standing gradient model, is attractive, but its weakness may be the postulation of an inward-directed sodium pump. The model proposed by Ernst and Mills (1977), although using an avian salt gland, might be more satisfactory. They suggested that the basolateral sodium pump, orientated to extrude sodium from the cell, could drive secretion in the epithelial cells of the salt gland by acting to maintain the sodium gradient from blood to cell. This would allow sodium to enter the cell down a favourable electrochemical gradient and would provide the driving force necessary for the transport of Cl^- into the cell against an electrical gradient. Once these ions have entered the cell, Cl^- then would be free to diffuse from the cell across the luminal membrane without the intervention of an apical pump, provided the cell interior is sufficiently electronegative to the lumen. Sodium, pumped into the intercellular space, would then follow through a shunt pathway, presumably across the tight junctions.

For the ultracytochemical detection of CAHase activity, the authors employed Yokota's technique (1969), which is a modification of Hansson's method (1967). Numerous electron-dense reaction products were observed in the microvilli of choroidal epithelial cells. Reaction deposits were also present in the basal infoldings, but to a lesser extent than in the microvilli. It is possible that at least a part of the membrane-localized CAHase might play a part in the penetration of CO_2 through the plasma membrane (Enns, 1967). These activities were completely inhibited by acetazolamide. From CAHase distribution in the epithelial cells, it can be surmised that the formation of H^+ and HCO_3^- from CO_2 is greater in the microvilli than in the basal infoldings. Intracellular H^+ exchanges extracellular Na^+ through the basal infoldings. HCO_3^- moves into the CSF mainly through the plasmalemma of the microvilli.

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DIFFERENTIAL SUSCEPTIBILITY OF HUMAN NEURAL CELL TYPES IN CULTURE TO INFECTION WITH HERPES SIMPLEX VIRUS

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SUMMARY

The ability of herpes simplex virus (HSV)-1 Glasgow (strain 17), HSV-2 (strain HG52), temperature sensitive mutants and a thymidine kinase negative mutant of Glasgow strain 17 to produce a cytopathic effect and induce viral antigen expression in primary and passaged human fetal brain cells was studied. No difference was detected between the behaviour of HSV-1 and HSV-2. Cell-type-specific markers and indirect immunofluorescence were used to define unambiguously the type of individual cells in culture. Cells characterized as astrocytes were present in passaged cultures. Neurons were only seen in primary cultures and were markedly nonpermissive for herpes simplex virus as defined by both cytopathic effect and antigen expression when compared with the other cell types. These techniques and observations are seen to have potential significance for a variety of clinical neurological and neurobiological studies.

INTRODUCTION

Studies of the susceptibility of cultured neural cells to herpes simplex virus (HSV) infection are important for a variety of reasons. First, it is well known that HSV is associated with human neurological disease. Herpes simplex encephalitis is the most serious of the neurological diseases caused by HSV, but other conditions such as aseptic meningitis and ascending myelitis have also been associated with this virus (Olson *et al.*, 1967; Klastersky *et al.*, 1972; Nahmias and Roizman, 1973; Finelli, 1975). Secondly, experimental studies have shown that HSV produces latent infections in the sensory ganglia of animals (Stevens, 1975), and latent HSV has been isolated from, and herpes virus information detected in, human ganglia (Baringer and Swoveland, 1973; Baringer, 1974, 1975; Forghani *et al.*, 1977; Warren *et al.*, 1977, 1978; Brown *et al.*, 1979). In addition, the combined use of dissociated nerve cell cultures with various techniques for the detection of viral products may provide a reliable *in vitro* model of HSV latency and give new insight into the lytic cycle in the preferred natural cellular environment of the virus.

It has recently become possible to identify unambiguously the major neural cell types in dissociated neural cell cultures from several species by the use of cell-type-specific antigenic markers (Raff *et al.*, 1979; Kennedy *et al.*, 1980). For example, the glial fibrillary acidic protein (GFAP) (Eng *et al.*, 1971), which is an intracellular protein associated with intermediate glial filaments (Bignami *et al.*, 1972; Schachner *et al.*, 1977), is detected only in astrocytes in central nervous system (CNS) cultures from many vertebrate species (Dahl and Bignami, 1973; Raff *et al.*, 1979), while the monoclonal antibody A2B5 reacts only with the surface of peripheral and central neurons in such cultures (Eisenbarth *et al.*, 1979; Walsh, 1980). The major myelin glycolipid galactocerebroside (GC) (Norton and Autilio, 1966) is a specific marker for oligodendrocytes (Raff *et al.*, 1978); and fibronectin (FN) (Wartiovaara *et al.*, 1974) can be used to identify fibroblasts and leptomeningeal cells in these cultures (Raff *et al.*, 1979). The great advantage of such cell-type-specific markers is that different cell types can be identified and quantitated even when they comprise a small proportion of the total cell population (Kennedy, 1982). Moreover, when combined with immunofluorescence studies using antibodies directed against specific viral antigens (*vide infra*), virally infected cells can be identified even when such cells show no morphological evidence of infection.

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It seemed pertinent to exploit these markers in HSV-infected human neural cell cultures since an analysis of the human cell specificity of HSV during a lytic infection clearly has more relevance to the relationship between HSV and its natural host than studies performed in animal cell cultures. Here we demonstrate for the first time that cell marker and virological techniques can be combined to define the behaviour of herpes simplex virus in both primary and serially passaged dissociated human neural cell cultures. Our findings would suggest that this system may provide a most relevant model in which to study HSV latency, and is also likely to have relevance to the study of HSV infections of the human nervous system.

MATERIALS AND METHODS

Virus

Wild-type (*ts*+ *syn* +) (nonsyncytial plaque morphology) and *ts* mutants (*syn* and *syn* +) (syncytial and nonsyncytial plaque morphology) of HSV-1 (Glasgow strain 17) and HSV-2 (HG52) were used as described previously (Timbury, 1971; Brown *et al.*, 1973). A temperature sensitive (*ts*) virus has a mutation which renders it unable to produce infectious progeny at 38.5° C (nonpermissive temperature) although it can still replicate normally at 31° C (permissive temperature), in contrast to wild type virus which can replicate at both temperatures. Immediately prior to use virus stocks were titrated in baby hamster kidney (BHK) 21/C13 cells (Macpherson and Stoker, 1962) at 31° C and 38.5° C.

Preparation of Cell Cultures

Baby hamster kidney (BHK 21/C13) cells were grown in Eagle's medium containing 10 per cent fetal calf serum and were dispersed on to glass coverslips as described below.

Dissociated primary neural cell cultures from 15 to 16 week old aborted human fetuses were prepared as previously described (Kennedy *et al.*, 1980). In brief, spinal cord, dorsal root ganglia or brain tissue, including cerebral hemispheres, were removed within 2 h from fetuses obtained at hysterotomy, digested in 0.25 per cent trypsin and 0.02 per cent collagenase (Worthington) and dissociated by trituration through a Pasteur pipette or a 23 gauge hypodermic needle. The resulting cell suspension was plated on to 13 mm glass coverslips in Dulbecco's Eagle's medium (DMEM) containing 20 per cent fetal calf serum and 25 μg/ml gentamicin in Linbro multiwell plates (Flow Laboratories). For dorsal root ganglia and brain cultures the KCl concentration was raised to 25 mM to promote neuronal growth. Cells were studied between the third and seventh day in culture.

Some primary whole brain cultures were used to produce passaged cells by splitting cultures 1:2 and growing in DMEM 20 per cent fetal calf serum. Cells were used at the first (P_1), second (P_2) or third (P_3) passage.

Virus Infection of Cell Cultures

Human neural cells growing on coverslips (10^4 cells/coverslip) were infected with virus at a multiplicity of infection (MOI) of 10 plaque-forming units per cell. After absorption for one hour at the appropriate temperature, the virus inoculum was removed, the coverslips washed twice and refed with fresh DMEM containing 10 per cent fetal calf serum. The cultures were then incubated at 31° C and 38.5° C (mutants) and 37° C or 38.5° C (wild type). In every experiment BHK 21/C13 cells were infected simultaneously.

Antisera

Polyspecific rabbit HSV antiserum raised against whole virus was a gift from Dr H. Marsden. A monoclonal antibody (1086) reacting with HSV glycoprotein D (anti-gD) was a gift from Dr J. Palfreyman. Rabbit anti-GFAP serum (Pruss, 1979), rabbit antifibronectin serum (Wartiovaara *et al.*, 1974), rabbit anti-GC serum (Raff *et al.*, 1979) and a monoclonal antibody (A2B5), reacting with central and peripheral neurons (Eisenbarth *et al.*, 1979; Walsh, 1980) were gifts from Drs R. Pruss, E. Ruoslahti, M. Raff and F. Walsh, respectively.

Antibody binding was visualized with sheep antirabbit IgG conjugated to fluorescein (Wellcome), goat antirabbit IgG conjugated to rhodamine (Nordic), rabbit antimouse IgG conjugated to fluorescein (Miles-Yeda) or goat antimouse IgG conjugated to rhodamine (Cappel).

Indirect Immunofluorescence Assay

Indirect immunofluorescence was performed as previously described (Brockes *et al.*, 1977; Raff *et al.*, 1979). The cultures growing on coverslips were studied at both 6 and 24 h after virus absorption. Cultures were incubated either with a polyspecific rabbit HSV antiserum (diluted 1:50) or anti-gD antibody (neat) for 30 min at room temperature, washed in phosphate-buffered saline and then exposed to the appropriate fluorescent conjugate for 30 min. Cultures were fixed in 5 per cent glacial acetic acid in 95 per cent ethanol (acid-alcohol) either before or after staining with HSV antiserum. In double labelling experiments other than with GFAP, human cultures were labelled simultaneously with cell-specific marker and viral-specific antibodies, for example, A2B5 antibody and rabbit HSV antiserum followed by a mixture of the two appropriate rhodamine and fluorescein-conjugated antibodies. In double labelling experiments with GFAP, cells were first stained live with rabbit HSV antiserum or anti-gD antibody, fixed in acid-alcohol and then stained for GFAP (Raff *et al.*, 1979). The conjugates were checked as previously described (Raff *et al.*, 1979) to ensure that they did not react with Ig of the inappropriate species. Both the percentage of cells showing a cytopathic effect and fluorescent staining were assessed when the cultures were examined under a Leitz Ortholux fluorescence microscope equipped with epi-illumination and phase contrast optics.

RESULTS

1. Primary Fetal Neural Cultures

The use of cell-specific markers allows the identification of the cell types present in dissociated cultures. The present studies use tissue derived from three anatomical regions (1) dorsal root ganglia, (2) spinal cord and (3) brain tissue. Table 1 shows that the proportions of the different cell types recovered vary considerably depending on the site from which the cells were derived. Dorsal root ganglion cultures contain approximately 30 per cent neurons (A2B5$^+$), 40 per cent fibroblasts (FN$^+$) and no astrocytes (GFAP$^+$). Schwann cells (30 per cent) were identified in these cultures by their bipolar morphology and their failure to bind any of the cell markers. Spinal cord cultures contained the lowest proportion of A2B5$^+$ neurons ($\sim$ 10 per cent) with a morphology comparable to dorsal root ganglia neurons, the highest proportion of fibroblasts (50 to 60 per cent); 25 per cent of the cells were identified as GFAP$^+$ astrocytes. The method of preparing brain tissue gave cultures in which over half the cells were A2B5$^+$ neurons (fig. 1). Remaining cells were astrocytes (30 per cent) and fibroblasts (10 per cent).

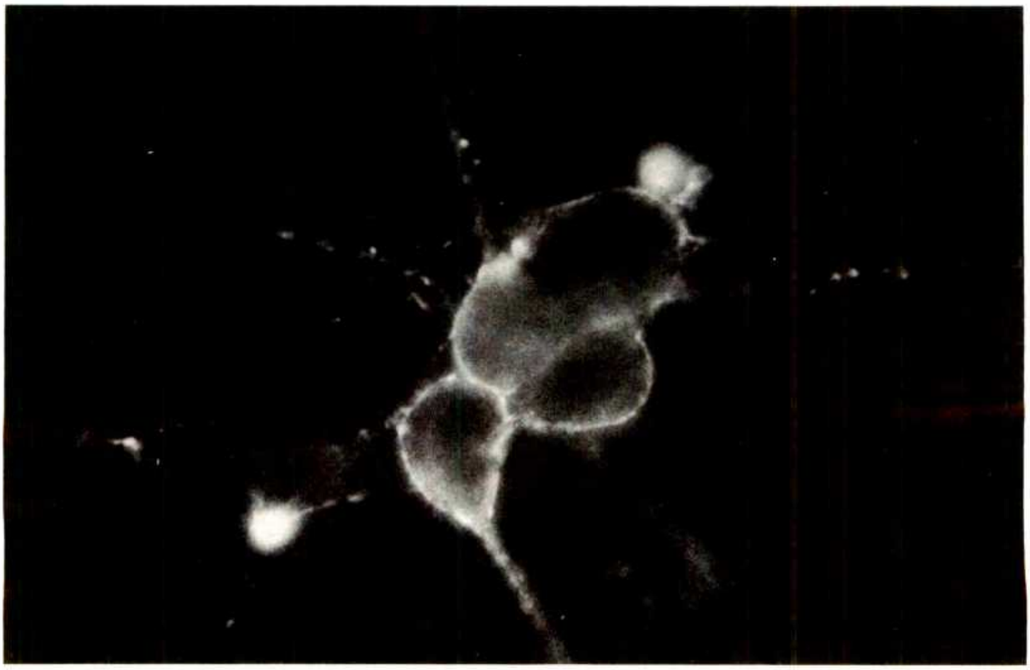

FIG. 1. A2B5$^+$ neurons in human brain culture. After five days in culture cells were labelled with A2B5 monoclonal antibody followed by rabbit antimouse IgG conjugated to fluorescein and viewed with fluorescence optics.

TABLE 1. IDENTIFICATION OF HUMAN NEURAL CELL TYPES IN PRIMARY CULTURE AND THE MORPHOLOGICAL CHANGES TAKING PLACE AFTER INFECTION WITH HSV

Culture	Virus MOI 10 PFU/cell	Incubation temperature (°C)	Percentage of cells in uninfected cultures				Percentage of cells in infected cultures at 24 h				Percentage loss of identifiable		
			Neurons	Astrocytes	Fibroblasts	Unidentified	Neurons	Astrocytes	Fibroblasts	Unidentified	Neurons	Astrocytes in infected cultures at 24 h	Fibroblasts
DRG	ts^{+} syn^{+}	37	30	—	40	30*	15/20	—	15/20	> 60	33/50	—	50/62
SC	ts^{+} syn^{+}	37	10	25/30	50/60	< 10	2/5	10	20	> 65	50/80	60/66	60/66
SC	*ts* G syn^{+}	38.5	10	25/30	50/60	< 10	5	10	30	55	50	60/66	40/50
SC	*ts* G syn^{+}	31	10	25/30	50/60	< 10	2	5	10/15	> 80	80	80/83	75/80
BT	*ts* K syn^{+}	38.5	50/60	30/40	10	< 10	50/60	30/40	10	< 10	0	0	0
BT	*ts* K syn^{+}	31	50/60	30/40	10	< 10	50/60	30/35	10	< 10	0	0	0

In all experiments at least 150 cells were counted on each coverslip. * Schwann cells on the basis of their bipolar morphology. DRG = dorsal root ganglion. SC = spinal cord. BT = brain tissue. MOI = multiplicity of infection. PFU = plaque-forming units.

TABLE 2. HSV ANTIGEN EXPRESSION IN HUMAN NEURAL CELL TYPES IN PRIMARY CULTURE

Culture	Virus MOI 10 PFU/cell	Incubation temperature (°C)	Percentage of cells showing CPE at 24 h	Percentage of cells labelled with rabbit anti-HSV at 24 h	Percentage of cells labelled with rabbit anti-HSV at 24 h			Percentage of cells labelled with anti-gD at 24 h	Percentage of cells labelled with anti-gD at 24 h		
					Neurons	Astrocytes	Fibroblasts		Neurons	Astrocytes	Fibroblasts
DRG	ts^{+} syn^{+}	37	50	80	50	—	80/90	60	30	—	60/70
BHK	ts^{+} syn^{+}	37	60	90				90			
SC	ts^{+} syn^{+}	37	70	90	50	75	90	80	40	40	80/85
BHK	ts^{+} syn^{+}	37	80/90	95				90			
SC	*ts* G syn^{+}	38.5	50	80	30	50	80	ND	ND	ND	ND
BHK	*ts* G syn^{+}	38.5	80	80				ND			
SC	*ts* G syn^{+}	31	80	90	20/30	50	90	90	2	20	80/90
BHK	*ts* G syn^{+}	31	90	90				80/90			
BT	*ts* K syn^{+}	38.5	0	5/10*	0	5	< 5	0	0	0	0
BHK	*ts* K syn^{+}	38.5	50	50				0			
BT	*ts* K syn^{+}	31	5	25*	5	50	< 5	0	0	0	0
BHK	*ts* K syn^{+}	31	70	75				50/60			

In all experiments at least 150 cells were counted on each coverslip. DRG = dorsal root ganglion. BHK = baby hamster kidney cells. SC = spinal cord. BT = brain tissue. * weak. ND = not done. CPE = cytopathic effect. MOI = multiplicity of infection. PFU = plaque-forming units.

In all cultures, a small proportion (less than 10 per cent) of cells failed either to label with any of the markers used or to have the characteristic morphology of Schwann cells. This has been reported previously (Kennedy *et al.*, 1980) and the identity of these cells is not known. As the fetuses used for these experiments were less than 16 weeks old, the galactocerebroside marker (GC) could not be used to identify oligodendrocytes, as GC is not expressed in human fetal cultures of this age (Kennedy, 1980).

2. *Effect of Infection with HSV on the Proportion of Cell Types in Primary Neural Cell Cultures*

Cultures of dorsal root ganglia, spinal cord and brain were either infected at an MOI of 10 PFU/cell with *ts*$^+$ *syn*$^+$ virus or *ts* mutants or left as uninfected controls. After incubation for 24 h at the appropriate temperatures, the cells were stained and the percentage loss of the various cell types from each culture was calculated by comparing the infected cultures with equivalent uninfected controls (Table 1).

In dorsal root ganglia cultures infected with *ts*$^+$ *syn*$^+$ virus at an MOI of 10 PFU/cell, the number of cells expressing A2B5 at 24 h was reduced to half that of the uninfected control cultures (30 per cent). The cytopathic effect observed was deterioration in the quality of the cultures, rounding up of cells, loss of distinct cell morphology and detachment of cells. The proportion of A2B5$^+$ positive cells (neurons) surviving lytic infection was somewhat higher than that observed for the Schwann cells in the cultures. At 24 h after infection more than 60 per cent of cells expressed no detectable marker. When an MOI of 40 was used to infect dorsal root ganglian cultures, 90 per cent of the total cell population was destroyed by 24 h but greater than 75 per cent of the surviving cells were neurons.

Spinal cord cultures infected with either *ts*$^+$ *syn*$^+$ or *ts* G *syn*$^+$ showed a proportionate loss of the three cell types at both 31° C and 37° C or 38.5° C and an accumulation of cells failing to label with any of the cell-specific markers used.

At the permissive temperature, about 80 per cent of the cells infected with *ts* G *syn*$^+$, although identifiable on morphological grounds, could no longer be classified by specific staining. In this respect *ts* G *syn*$^+$ was more cytopathic (only 20 per cent of cells being positively identified by cell markers) than *ts*$^+$ *syn*$^+$ virus where nearly half the cells could still be identified by specific markers at 24 h post-infection.

By 24 h brain cultures infected with *ts* K *syn*$^+$ at 31° C and 38.5° C showed no loss of cells identified by the specific markers. *Ts* K *syn*$^+$ was relatively noncytopathic for this culture at either temperature.

In infected cultures, cells which are no longer identifiable comprise (1) dead cells, (2) rounded up cells (making the use of cell markers or morphology for identification of types impossible) and (3) infected cells which have suffered possible concomitant loss of cell markers on acquisition of viral antigens. Any cells that had fallen off the coverslips could not be scored.

3. *HSV Antigen Expression in Primary Cultures*

At 6 and 24 h after infection with either *ts*$^+$ *syn*$^+$ or *ts* mutants cultures were examined for gross cytopathic effect and HSV antigen expression detected by immunofluorescence, using either a polyspecific antiserum or a monoclonal antibody directed against gD. Two fluorochrome immunofluoresence allowed estimation of the proportion of the three identifiable cell types expressing HSV antigens.

At 6 h post-infection, very little cytopathic effect was detectable except after infection with *ts* G *syn*$^+$ at both 31° C and 38.5° C. By 24 h more than 50 per cent of the BHK, dorsal root ganglia and spinal cord cultures were showing cytopathic effect, whereas in brain cultures infected with *ts* K *syn*$^+$ virtually no cytopathic effect was evident at either temperature (Table 2).

Virus antigen expression at 6 h was weak in 70 to 80 per cent of cells infected with *ts*$^+$ *syn*$^+$ virus and in 80 to 90 per cent of cells infected with *ts* G *syn*$^+$. No antigen was detectable in *ts* K *syn*$^+$ infected cultures at this time.

By 24 h post-infection with *ts*$^+$ *syn*$^+$ at either the permissive or nonpermissive temperatures, 60 to 90 per cent of the total cell population of dorsal root ganglion or spinal cord or BHK expressed viral antigens as detected either by the polyspecific HSV antiserum or by the anti-gD monoclonal antibody (Table 2). After *ts* G *syn*$^+$ infection at the permissive or nonpermissive temperatures, virus antigens were detectable in the majority of both spinal cord and BHK cells using polyspecific HSV antiserum. Infection of brain cultures which were composed of more than 50 per cent neurons with *ts* K *syn*$^+$ gave very weak staining with the polyspecific serum in a small proportion of cells at both the nonpermissive and permissive temperatures. No cells positive for anti-gD were present in brain cultures infected with *ts* K *syn*$^+$ at either temperature. At both 31° C and 38.5° C, 50 to 60 per cent of the *ts* K *syn*$^+$ infected BHK cells expressed virus antigens as detected by the polyspecific antiserum. After infection with *ts* K *syn*$^+$, as expected, 75 per cent of BHK cells expressed gD at the permissive temperature but at the nonpermissive temperature expression of gD was not detectable.

These results have been analysed in terms of the classes of cells expressing virus antigen. Cells identified as astrocytes and fibroblasts behaved similarly to BHK cells (fig. 2) with virtually every cell expressing HSV antigens 24 h after infection. However, irrespective of (1) whether *ts*$^+$ or *ts* virus was used for infection or (2) the source of the cultured cells the proportion of neurons expressing viral antigens is markedly lower than that observed with other cell types (fig. 3). For example, in *ts* G *syn*$^+$ infection of spinal cord, 25 per cent neurons, 50 per cent astrocytes and 90 per cent of the fibroblasts showed positive staining with HSV antiserum and 2, 20 and 90 per cent, respectively, with anti-gD, and in brain culture infection with *ts* K *syn*$^+$ at 31° C, 5 per cent of neurons and 50 per cent of astrocytes expressed HSV antigens. Fig. 4 shows an astrocyte in a spinal cord culture infected with *ts*$^+$ *syn*$^+$ virus in which the astrocyte has been identified by GFAP staining and viral antigen detected

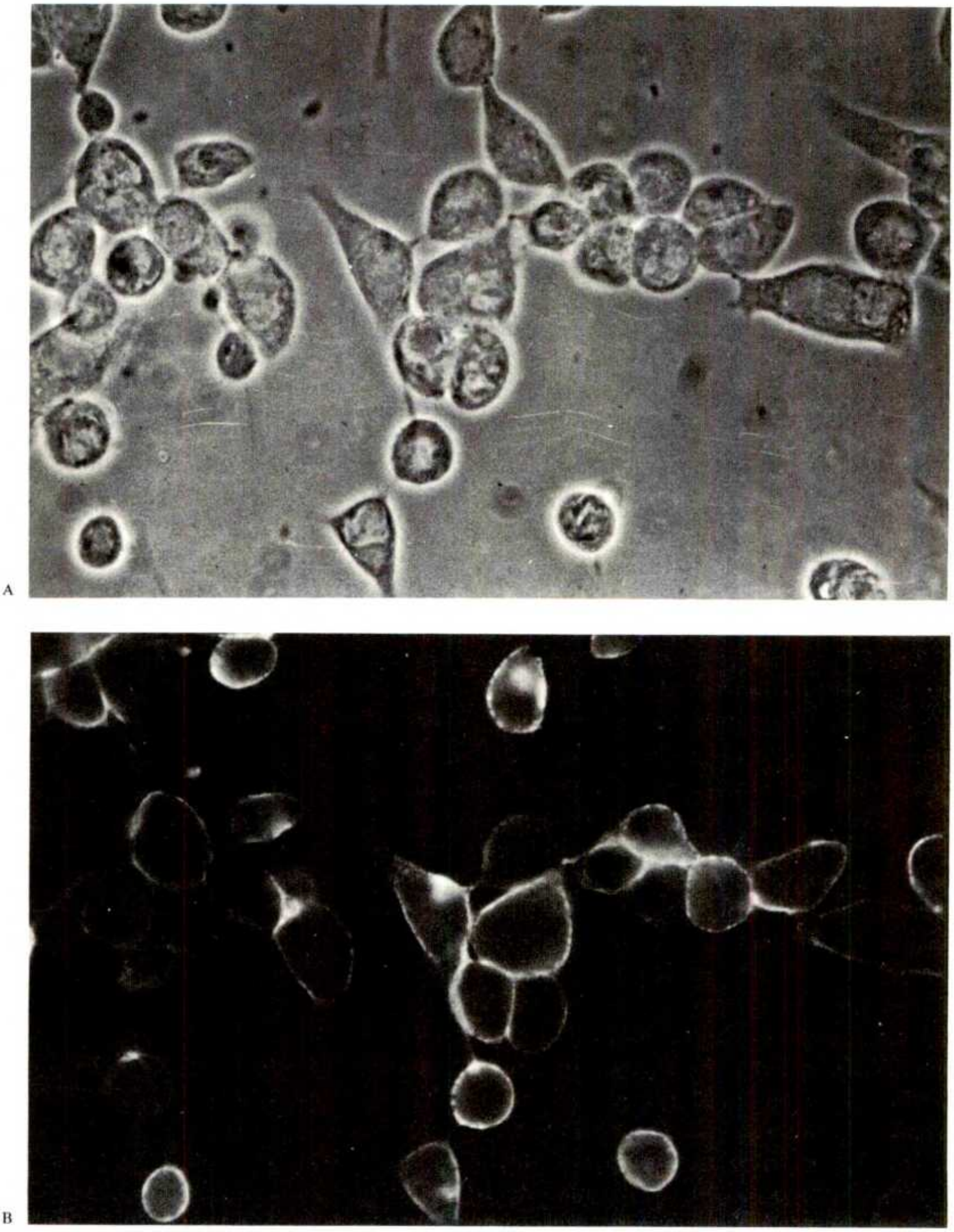

FIG. 2. BHK21/C13 cells labelled with anti-gD monoclonal antibody. 24 h after infection with 10 PFU/cell of HSV-1, the cells were labelled with anti-gD followed by rabbit antimouse IgG conjugated to fluorescein and viewed with phase contrast (A) or fluorescence (B) optics. Note the uniform and regular fluorescent staining on virtually every cell.

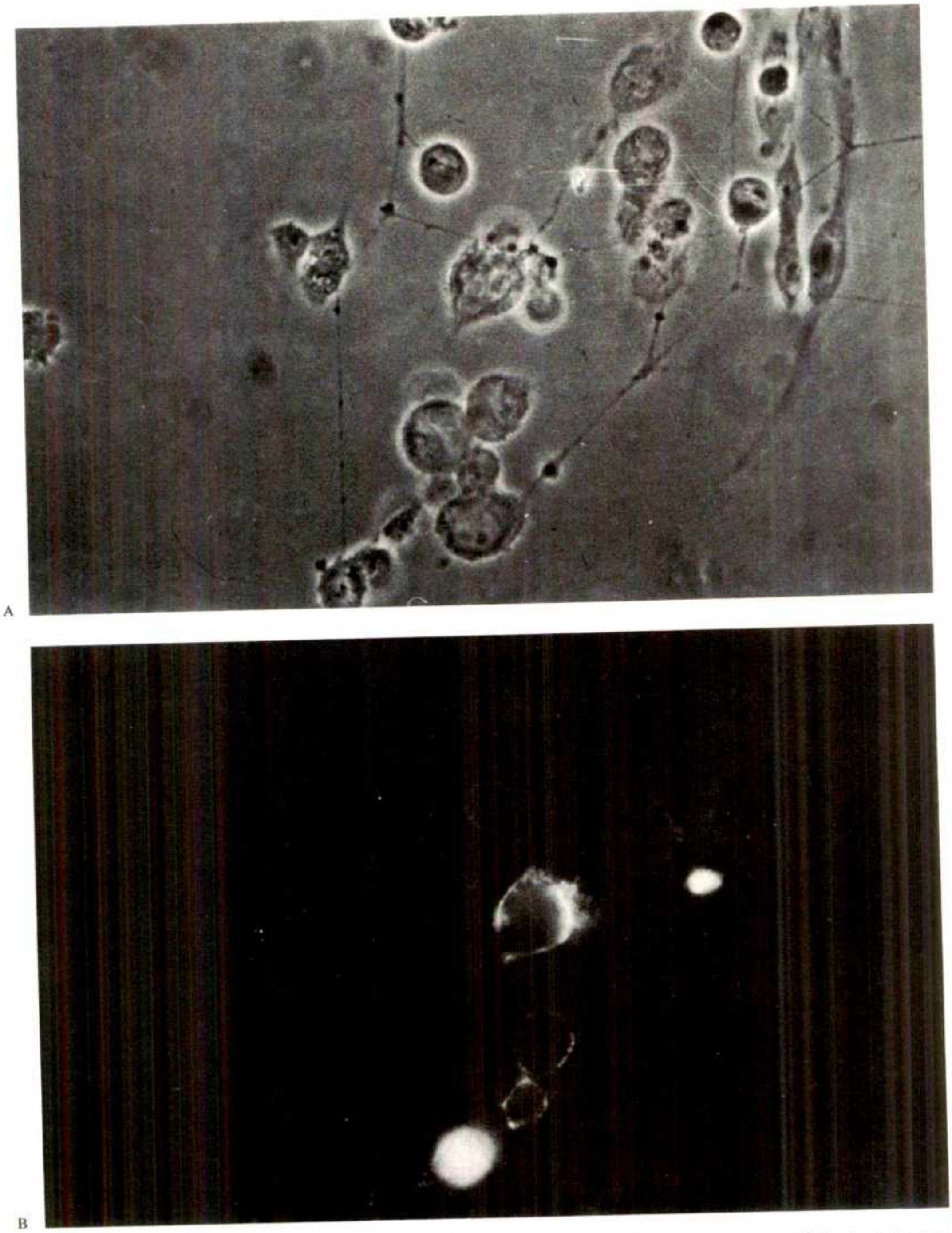

FIG. 3. Labelling of infected human dorsal root ganglion cells with rabbit anti-HSV antiserum. 24 h after infection with 10 PFU/cell of HSV-1, cells of human dorsal root ganglion cultures were labelled with rabbit anti-HSV followed by sheep antirabbit IgG conjugated to fluorescein and viewed with phase contrast (A) and fluorescence (B) optics. Note that the majority of process-bearing neurons are not stained by rabbit anti-HSV antiserum.

by the anti-gD monoclonal antibody. It would appear that either neurons are less susceptible to infection with HSV, or that they take longer to express antigen or that the virus is present in the neurons in a form in which antigen expression is suppressed.

4. Passaged Human Fetal Brain Cultures

Dissociated fetal brain tissue was put into culture as described for primary cells. After about seven days in culture when the monolayers were semiconfluent, the cells were split 1 : 2 and passaged at intervals. It has been possible to obtain primary lines from these cultures which have so far in some cases continued to at least passage No. 31. The proportion of marker identified cell types in the cultures up to passage 5 are shown in Table 3. The two main cell types surviving after the first passage were astrocytes and fibroblasts. Neurons, as expected, could not be detected in passaged cells. With increasing passage number, the proportion of astrocytes decreased and the proportion of fibroblastic cells increased. The cultures also contained cells which could not be identified either by immunofluoresence or morphology.

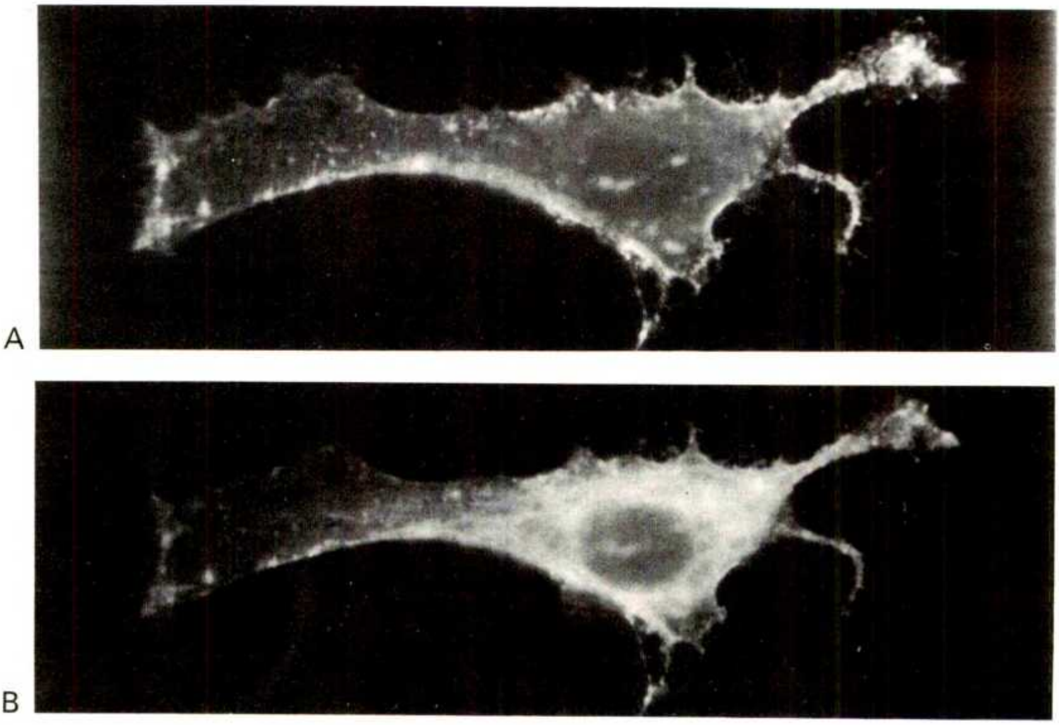

FIG. 4. Anti-gD$^+$/GFAP$^+$ cell in infected human spinal cord culture. 24 h after infection with 10 PFU/cell of HSV-1, cells in primary human spinal cord cultures were labelled with anti-gD monoclonal antibody followed by rabbit antimouse IgG conjugated to fluorescein and fixed in acid-alcohol. After washing they were incubated with rabbit anti-GFAP followed by goat antirabbit IgG conjugated to rhodamine and viewed with fluorescein (A) or rhodamine (B) optics. The cell shows surface staining with anti-gG antibody and characteristic intracellular staining with anti-GFAP serum.

5. *Growth of HSV in Passaged Human Fetal Brain Cells*

Insufficient primary human fetal brain (FHB) cultures were available to perform one step growth experiments. To determine if HSV was replicating in passaged human cells, one step growth experiments using both wild type and mutant virus were carried out using low passage fetal brain cultures and BHK cells as controls. An MOI of 2 PFU/cell was used and the cultures were harvested at intervals up to 30 h post-infection. Fig. 5 shows the one step growth curve for *ts*$^+$ virus in FHB and BHK cells. The timing of production of infectious virus in both was very similar and the yield of infectious virus by 24 h in FHB cells was 3 logs higher than the input virus at time zero. One step growth curves of *ts* virus at the permissive temperature gave similar patterns. This confirms that FHB cells readily support a lytic cycle whose parameters are very similar to those seen in BHK cells. Virus antigen expression monitored by fluorescent antibody staining detects synthesis of virus coded polypeptides but cannot be used as evidence for the assembly of infectious virus progeny.

6. *Expression of HSV Antigens in Passaged Human Fetal Brain Cells*

Human fetal brain cultures (P1-P3) were separately infected with wild type virus and a range of *ts* mutants at the permissive and nonpermissive temperatures. BHK cells were used as controls. Expression of viral antigens at 6 and 24 h post-infection was detected by fluorescent antibody staining using polyspecific HSV antiserum. Using two fluorochrome immunofluorescence, the proportion of GFAP$^+$/HSV$^+$ astrocytes in the cultures could be determined.

GFAP$^+$ astrocytes comprised 20 to 40 per cent of the total cell population in uninfected cultures at all passage numbers. By 24 h after infection with either *ts*$^+$ or *ts* virus, this percentage was reduced to between 2 to 10 per cent of the total population. The majority of surviving astrocytes, however, expressed viral antigens at both 31° C and 38.5° C irrespective of the mutant used. The proportions of virus antigen positive astrocytes (HSV$^+$/GFAP$^+$) in these cultures infected with mutant virus was much greater than the percentage positive after infection with *ts*$^+$ *syn*$^+$ virus. The fact that all the mutant stocks used had higher particle : PFU ratios than the *ts*$^+$ *syn*$^+$ stock may have contributed to these observations.

TABLE 3. PROPORTION OF MARKER-IDENTIFIED CELL TYPES IN PASSAGED FETAL HUMAN BRAIN (FHB) CULTURES

Passage No.	*Percentage of cells expressing GFAP**	*Percentage of cells expressing fibronectin*	*Percentage of GFAP-negative fibronectin-negative cells*
1 (FHB 13)	20–30	60–75	10
2 (FHB 11)	25–40	50–60	10–15
3 (FHB 11)	20–40	60–70	15–20
4 (FHB 11)	15–20	60–70	15–20
5 (FHB 11)	15–20	70–75	15–20

In all experiments, number of cells counted was at least 150 cells per coverslip. *Figures given are ranges of at least three separate experiments in the case of GFAP assays and ranges of either one or two experiments for other assays.

TABLE 4 MORPHOLOGICAL CHANGES AND ANTIGEN EXPRESSION IN PASSAGED HUMAN FETAL BRAIN CELLS AFTER INFECTION WITH HSV

Culture	*Virus MOI 10 PFU/cell*	*Incubation temperature (° C)*	*Percentage of cells showing CPE at 24 h*	*Percentage of cells labelled with rabbit anti-HSV*		*Percentage of GFAP*$^{+}$ *cells labelled with rabbit anti-HSV at 24 h*
				6 h	*24 h*	
FHB	*ts*$^{+}$ *syn*$^{+}$	37	50	70*	70	20/30
BHK	*ts*$^{+}$ *syn*$^{+}$	37	40/50	90*	75	—
FHB	*ts*$^{+}$ *tk*$^{-7}$	38.5	50/60	0	85	90
BHK	*ts*$^{+}$ *tk*$^{-7}$	38.5	70	80	90	—
FHB	*ts*$^{+}$ *tk*$^{-7}$	31	30/40	0	70	50
BHK	*ts*$^{+}$ *tk*$^{-7}$	31	50/60	80*	90	—
FHB	*ts* G *syn*$^{+}$	38.5	60/70	50/60	70	ND
BHK	*ts* G *syn*$^{+}$	38.5	80	50	75	—
FHB	*ts* G *syn*$^{+}$	31	90	80*	90	ND
BHK	*ts* G *syn*$^{+}$	31	80	80/90*	80	—
FHB	*ts* H *syn*$^{+}$	38.5	30	0	85	70
BHK	*ts* H *syn*$^{+}$	38.5	30	50	80/90	—
FHB	*ts* H *syn*$^{+}$	31	50	0	80	80
BHK	*ts* H *syn*$^{+}$	31	50/60	70	80/90	—
FHB	*ts* I *syn*	38.5	60	0	70	80
BHK	*ts* I *syn*	38.5	60	70	70	—
FHB	*ts* I *syn*	31	80	0	90	80
BHK	*ts* I *syn*	31	90	80/90	90	—
FHB	*ts* K *syn*$^{+}$	38.5	0	0	60*	50
BHK	*ts* K *syn*$^{+}$	38.5	30	40/50*	50	—
FHB	*ts* K *syn*$^{+}$	31	50	0	60	80
BHK	*ts* K *syn*$^{+}$	31	70	80*	80	—
FHK	*ts* L *syn*$^{+}$	38.5	70	70/80	90	60
BHK	*ts* L *syn*$^{+}$	38.5	70/80	50	80	—
FHB	*ts* L *syn*$^{+}$	31	70/80	70/80*	90	60
BHK	*ts* L *syn*$^{+}$	31	80/90	80	90	—
FHB	*ts* S *syn*$^{+}$	38.5	50	0	50	50
BHK	*ts* S *syn*$^{+}$	38.5	60	50	70	—
FHB	*ts* S *syn*$^{+}$	31	60/70	0	70/80	80
BHK	*ts* S *syn*$^{+}$	31	80/90	75	80/90	—
FHB	HG52	38.5	60	ND	80	60
BHK	HG52	38.5	90	ND	90	—
FHB	HG52	31	30	ND	70	50
BHK	HG52	31	50	ND	50/60	—
FHB	*ts* 5	38.5	30	ND	80	50
BHK	*ts* 5	38.5	40	ND	50	—
FHB	*ts* 5	31	30/40	ND	70	50
BHK	*ts* 5	31	80	ND	70/80	—

In all experiments at least 150 cells were counted on each coverslip. ND = not done. FHB = fetal human brain. BHK = baby hamster kidney cells. * weakly positive. CPE = cytopathic effect. MOI = multiplicity of infection. PFU = plaque-forming units.

Two general patterns of infection were observed in lytically infected passaged cells (Table 4). The first type was observed with *ts*$^{+}$ *syn*$^{+}$, *ts* G *syn*$^{+}$ and *ts* L *syn*$^{+}$ and consisted of CPE in approximately 30 per cent of the total cell population and weak viral antigen expression in most cells at 6 h. A marked cytopathic effect and strong staining for antigen in the vast majority of cells was seen by 24 h post-infection. As expected, these changes were more marked at the permissive temperature. The second pattern was seen with *ts*+ *tk*−7 (thymidine kinase deficient) (Jamieson and Subak-Sharpe, 1978), *ts* H *syn*+, *ts* I *syn*, *ts* K *syn*+ and *ts* S *syn*+. In these infections, neither cytopathic effect nor antigen expression was observed at 6 h but was seen in the majority of cells by 24 h. *Ts*+ *tk*−7 behaved anomalously as it would be assumed that this virus should behave as wild type virus in these cultures of replicating cells which would supply the cellular thymidine kinase.

The result with *ts* K *syn*+ is noteworthy. In passaged cultures infected at 38.5° C, 60 per cent of the cells showed weak staining with HSV antiserum, whereas in primary cultures of whole brain in which 50 to 60 per cent of cells were classified as

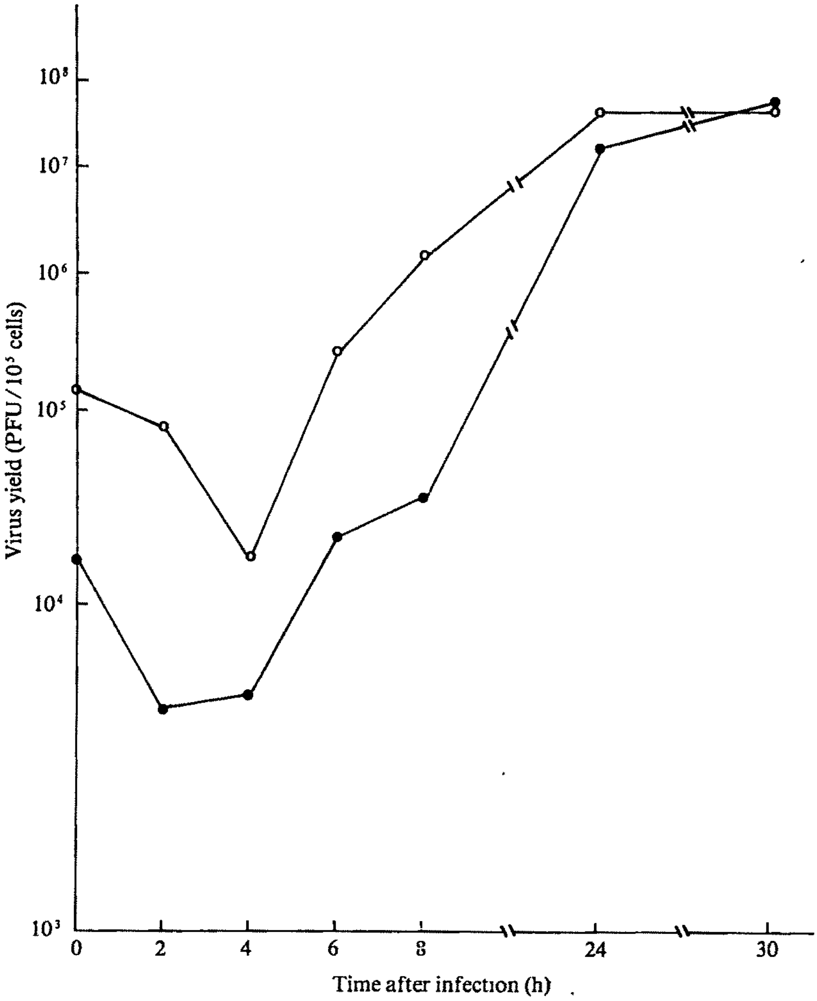

FIG. 5. One-step growth curves of HSV-1 in BHK and FHB cells One step growth curves of HSV-1 wild type virus (*ts*+ *syn*+) in fetal human brain (FHB) cells (open circles) and BHK21/C13 cells (filled circles). Cells were infected at a multiplicity of infection of 2 PFU/cell and incubated at 37° C. At various times post-infection, cultures were harvested and the virus released from the cells by sonication. Virus yields were titrated on BHK21/C13 cells at 37° C.

neurons, similar infections led to only 5 to 10 per cent of the cells staining weakly for virus antigen (Table 2). It is our impression that the susceptibility of these fetal brain cell cultures to HSV infection may depend on the percentage of neurons in the cultures, but at present we have no satisfactory explanation for this finding. There was no difference in the behaviour of *ts*$^+$ *syn*$^+$ and *ts* G *syn*$^+$ in primary and passaged cultures.

The wild type HSV-2 strain HG52 and a *ts* mutant derived from it, *ts* 5, were also examined. HG52 behaved similarly to the *ts*$^+$ *syn*$^+$ HSV-1 strain 17. The cytopathic effect after infection with *ts* 5 only affected 30 per cent of cells at 24 h but 70 per cent or more of cells expressed HSV antigens detectable with polyspecific HSV antiserum.

DISCUSSION

The combined use of cell-type-specific markers, antibodies to HSV-specific antigens and recently developed human nervous tissue culture techniques in characterizing the pattern of HSV infection of human neural cells has not been previously exploited. Former studies have been concerned with HSV infection of normal neural cells in dissociated (Rajcani and Scott, 1972), explanted (Baringer, 1974, 1975; Warren *et al.*, 1977, 1978) and suspension cultures (Vahlne *et al.*, 1978), as well as cell lines derived from neuroblastomas (Schwartz and Elizan, 1973; Gerdes *et al.*, 1979), organized nerve tissue (Feldman *et al.*, 1968; Bornstein *et al.*, 1969; Leestma *et al.*, 1969; Dubois-Dalcq *et al.*, 1972; Fournier *et al.*, 1977; Ecob-Johnston *et al.*, 1978, 1979) and transformed nerve cells (Lancz and Zettlemoyer, 1976). In these studies, however, neural cells were not positively identified with markers. The present study using specific markers has allowed unambiguous identification and quantitation of the human neuronal and glial cell types which support HSV replication. The growth curve patterns demonstrated that HSV was actually replicating in such cultures.

It is notable that central and peripheral neurons were more restrictive for wild type HSV than astrocytes, Schwann cells and fibroblasts. More neurons survived an infection and relatively few surviving neurons expressed viral antigens at 24 h after infection. The experimental design only permitted the use of mixed populations of cells—it was thus not possible to determine if neurons released infectious virus under these conditions. Morphological studies showed that a proportion of neurons in infected cultures exhibited typical cytopathic effect. This is consistent with the results of previous studies (Rajcani and Scott, 1972).

Cultures infected with *ts* G *syn*$^+$ induced a marked cytopathic effect both at the permissive and the nonpermissive temperatures; over 50 per cent of astrocytes and fibroblasts and 30 per cent of neurons were positively stained with rabbit HSV antiserum. Very few neurons, however, were stained with anti-gD in comparison with the other cell types.

We are aware that herpes simplex virus infection causes the induction of Fc receptors in cultured cells. However, this is very unlikely to cause cross-reaction in the immunofluorescence because of the very low abundance of this glycoprotein (gE) and its low binding affinity. This is confirmed by the different patterns of the fluorescence of the rhodamine and fluorescein conjugates in the material stained by two fluorochrome immunofluorescence (fig. 4).

In brain cultures none of the neurons supported the growth of the mutant *ts* K *syn*$^+$. There was no cytopathic effect either at the permissive temperature or nonpermissive temperature and significant antigen was detected in astrocytes only at the permissive temperature. The lack of antigen expression in neurons with this mutant at both the permissive and nonpermissive temperatures may relate to the processing defect noted by Gerdes *et al.* (1979) in neuroblastomas.

It is interesting that viral antigens were expressed mainly on the neuronal cell bodies rather than the processes emanating from them. This observation was more marked with monoclonal antibody directed against gD which is possibly a reflection of the larger number of viral antigens recognized by rabbit HSV antiserum compared with the single antigen specifically detected by the monoclonal anti-gD antibody. The HSV antiserum, in addition, allowed visualization of some antigens mainly at the surface of infected BHK cells under conditions in which only HSV coded immediate early polypeptides would be expected to be produced (cycloheximide block and release).

In order to assess the proportion of GFAP$^+$ astrocytes in primary and passaged cells which were infected with HSV, a comparison was made of the number of marker-identified cells with those in uninfected control cultures. The proportion of identified cells which were labelled with rabbit HSV antiserum and monoclonal anti-gD antibody was also determined. To some extent therefore, our methods were indirect since there was no means of knowing definitely the previous identity of individual cells showing a complete cytopathic effect. Moreover, when GFAP positivity was lost in experiments using wild type and mutant viruses, it was not possible to determine whether the astrocytes were preferentially killed or the cells survived but lost the GFAP antigen. It seems likely that at least some of the infected cells had lost GFAP during infection since a number of cells with astrocytic morphology were present in infected cultures showing a proportionally greater loss of GFAP$^+$ cells compared with the total cytopathic effect and very few GFAP$^+$/HSV$^+$ or GFAP$^+$/gD$^+$ cells showing cell degeneration were seen which is not what would be expected if all the astrocytes were selectively killed. Furthermore, in all experiments the presence of intact cells labelled with both cell marker antibodies and rabbit HSV antiserum indicates that viral antigen expression and cell death can be dissociated, and it seems likely that the former does not always lead to the latter.

Our study revealed marked differences in the cell specificity of HSV-1 mutants. Although *ts*$^+$ *tk*$^{-7}$, *ts* H *syn*$^+$, *ts* S *syn*$^+$ and *ts* I *syn* only produced a moderate cytopathic effect in passaged cells, both *ts* G *syn*$^+$ and *ts* L *syn*$^+$ were less restricted in human cells. It is noteworthy that these two mutants had lower particle:PFU (particle count:infectious particle) ratios than the others. *Ts* I *syn* did produce a marked cytopathic effect at 24 h, which is consistent with the 'leakiness' of this virus observed in other systems (Mechie, 1974). As would be expected from its behaviour in BHK cells, *ts* K *syn*$^+$ was the most impaired mutant tested in that it had no effect on central neurons and only produced a small amount of cytopathic effect at the permissive temperature in passaged cultures. Explanations for the heterogeneous patterns of infection may well emerge as our understanding of the molecular biological events occurring during lytic infection with these mutants increases.

The wild type and *ts* 5 of HSV-2 showed a pattern of infection very similar to that of HSV-1 and HSV-1 *ts* mutants. However, only passaged cells were available for a comparison of the behaviour of HSV-1 and HSV-2. Clinical evidence would suggest that HSV-1 is more neurovirulent than HSV-2 in adults (Stalden *et al.*, 1973; Nahmias and Roizman, 1973). Some experimental systems have yielded data supporting the concept of differences between HSV-1 and HSV-2 with neural cells (Vahlne *et al.*, 1979, 1980). Before definite conclusions can be drawn in our system a more extensive study is required, in particular the comparison of HSV-1 and HSV-2 after infection of primary human neural tissues.

Both the techniques used in this study and our observations on neural cell susceptibility to HSV infection have a number of implications for the investigation of nervous diseases caused by viruses. For example, knowledge of the factors influencing the usual restriction of HSV to particular nerve cell types *in vitro* may eventually help our understanding of the pathogenic mechanisms of virus induced nerve cell damage *in vivo*. It has been seen that human astrocytes and fibroblasts are more susceptible to lytic HSV infection than both central and peripheral neurons. Although the interpretation of these findings in relation to human disease is speculative at present, it is possible that in latent HSV infections the neuronal cell body may harbour latent HSV. Vahlne *et al.* (1978) have suggested that in the peripheral nervous system a low rate of virus production in the neurons might contribute to maintaining HSV infection in ganglia without significant progression. However, in order to develop a reliable *in vitro* model of HSV latency in neurons it will be necessary to maintain the human cultures for many weeks or months.

We observed differences in the behaviour in nervous system cultures of wild-type and mutant herpes viruses, but the biological significance of these differences is unclear. It would, however, be interesting to isolate HSV from severe cases of herpes simplex encephalitis and correlate clinical virulence with its ability to produce lytic and/or latent infection of nerve cells *in vitro*. In addition, our techniques are not limited to HSV since it should be possible to study the cellular specificities of other neurotropic viruses, providing appropriate antibodies to specific components of the virus or its products are available.

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EYE MOVEMENT DISORDERS IN MULTIPLE SCLEROSIS AND OPTIC NEURITIS

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SUMMARY

Horizontal saccadic and smooth pursuit eye movements were studied in 84 patients with multiple sclerosis (MS) and 21 patients with optic neuritis (ON). The MS patients were clinically classified as 'definite', 'probable', or 'possible'; subclinical eye movement disorder was found in 80 per cent of the definite, 74 per cent of the probable and 60 per cent of the possible category. Five of the ON patients (25 per cent) showed a subclinical eye movement deficit; these 5 were young patients with a recent history of ON. In a group of 27 MS patients with symptoms of spinal cord involvement only, 14 showed subclinical oculomotor disorder indicating the involvement of cerebral structures in the demyelination process. A study of the correlation between specific eye movement parameters and results of visual evoked response (VER) tests revealed that saccadic latency or smooth pursuit abnormalities are not correlated with prolonged VER latencies (P-100 peak latency). This indicates that lesions beyond the primary visual pathway contribute substantially to both parameters of oculomotor dysfunction.

A significant correlation was found between prolonged saccadic latency and smooth pursuit deficit. An explanation for this finding based on functional aspects of the saccadic and smooth pursuit systems and their mutual interaction is presented. The occurrence of internuclear ophthalmoplegia (INO) is significantly related to an increase of saccadic latency. This finding indicates that demyelination in the patients manifesting INO may not be restricted exclusively to one or both medial longitudinal fasciculi, but may extend to other brainstem structures which are functionally involved in the programming of saccades.

The findings confirm the value of standardized objective examination of eye movements in the detection and clarification of subclinical lesions in the central nervous system of patients with an early diagnosis of MS or ON.

INTRODUCTION

The development and application of objective noninvasive techniques for the monitoring of neurological function or disease activity is of increasing interest to clinicians, in particular, as diagnostic aids for the detection of diseases in which diagnosis is difficult, of which multiple sclerosis (MS) is perhaps the most important. The diagnosis of MS rests on objective evidence concerning the presence and the severity of at least two lesions in the central nervous system, which should preferably involve different functional and anatomical units (Schumacher *et al.*, 1965). On the basis of the clinical evidence, MS in a given patient may be classified as definite, probable or possible (McAlpine *et al.*, 1972). Various invasive and noninvasive methods for the detection of subclinical lesions are currently available to increase the certainty and reliability of the clinical diagnosis, and to provide additional support for the diagnosis in a monosymptomatic or early state of the disease. None of the techniques available today, however, is specific for the detection of demyelinating lesions. Laboratory cerebrospinal fluid (CSF) tests constitute the most commonly applied invasive method, while noninvasive evoked response examinations are frequently used to detect subclinical disorders of the visual (VER) (Halliday *et al.*, 1972), somatosensory (Namerow, 1968) or auditory brainstem system (Robinson and Rudge, 1980). Over the past five years, special interest has been shown in the study of eye movements as a noninvasive tool for the detection of subclinical lesions of the oculomotor system. A few studies of ocular kinetics in MS patients have been published (Mastaglia *et al.*, 1979; Tackmann *et al.*, 1980; Solingen *et al.*, 1977; Sharpe *et al.*, 1981). These investigators concluded that examination of eye movement is potentially most useful for the detection and localization of subclinical lesions of the oculomotor system of MS patients. Most of the patients studied, however, were in the definite MS category.

The objective of our study is the evaluation and quantitation of eye movement disorders in probable and possible MS patients and the provision of eye movement data on a group of patients suffering from optic neuritis. Visual loss caused by ON has been reported in about 30 to 40 per cent of MS patients at the onset or during the course of the disease (Hutchinson, 1976; Poser, 1979; Cohen *et al.*, 1979; Poser and Ritter, 1980; Wray, 1981). Visual impairment caused by ON may be the initial symptom of MS (Sandberg-Wollheim, 1975). In an extensive study based on 1271 MS patients (Wikström *et al.*, 1980), 17 per cent of the patients were found to have ON as the sole initial symptom of MS. This would seem to justify regarding any ON patient as a potential MS patient (Hutchinson, 1976; Nikoskelainen *et al.*, 1981). We therefore also studied eye movements in 21 patients with current or recent ON without any other symptoms relating to MS. Finally, oculomotor tests were performed on a group of MS patients with clinical symptoms of a focal lesion in the spinal cord to identify a second subclinical lesion in the central nervous system.

Both horizontal saccadic and smooth pursuit eye movements were studied. The primary objective of the study as a whole was the detection of specific oculomotor disorders such as prolonged saccadic latency, reduced saccade velocity, dissociated nystagmus in lateral gaze and defective smooth pursuit. Special attention was paid to anatomical and functional relationships between coexisting oculomotor disorders, and to assess the contribution of the study of individual oculomotor disorders to an increase in diagnostic certainty for MS and ON.

MATERIAL AND METHODS

Patients

Eye movements were studied in 84 MS patients (including 30 males) and 21 ON patients (including 10 males) over the period of a year. The MS patients were classified as having definite, probable or possible MS according to criteria proposed by McAlpine *et al.* (1972). The ON patients complained of loss of vision in one or both eyes with partial or total recovery within days or months without any other symptoms referrable to MS. The general status of the MS and ON patients as determined just prior to the time of the oculomotor investigations is summarized in Table 1. These data include an assessment of the patient's level of disability according to the Disability Status Scale (DSS) of Kurtzke (1965).

TABLE 1 GENERAL CHARACTERISTICS OF PATIENTS WITH A HISTORY OF MULTIPLE SCLEROSIS (MS) AND OPTIC NEURITIS (ON)

						No of patients with			
Clinical category	*No of patients*	*Mean age (yrs)*	*Range (yrs)*	*Mean disease duration (yrs)*	*Range (yrs)*	*ON*	*Spinal cord involvement*	*Clinically abnormal eye movements*	*Mean Kurtzke DSS score*
Definite MS	28	48 (16)	24–76	14.5 (12)	2–40	6	16	7	6.7 (1.4)
Probable MS	30	41 (13)	20–62	7.6 (8)	1–25	9	9	3	3.7 (2.1)
Possible MS	26	37 (14)	15–63	5.1 (6)	1–24	3	2	—	1.6 (1.1)
Total MS	84	42 (15)	15–76	8.7 (11)	1–40	18	27	10	4.0 (1.9)
ON	21	30 (13)	11–50	2.8 (2)	0.1–7	21	—	—	— (—)

The numbers in brackets represent standard deviations (SD) DSS = Disability Status Scale

Methods

The (portable) equipment used to measure eye movements in the present study was designed in the Department of Medical Physics of the Vrije Universiteit, Amsterdam, and is currently used for a wide range of eye movement investigations in connection with various neurological diseases. Some preliminary clinical applications have also given good results. While it borrows certain elements from the techniques described by previous authors (Solingen *et al.*, 1977; Mastaglia *et al.*, 1979; Tackmann *et al.*, 1980; Sharpe *et al.*, 1981) it may be regarded as a new test procedure.

The chief improvements introduced in our procedure were the following: placing of electrodes on both canthi of both eyes for more comprehensive following of eye movements; random presentation of stimuli for saccadic eye movement to avoid anticipation effects; comparison of test results with measures of severity of MS disorder; comparison of both reaction time and accuracy of eye movements on the one hand and eye movement velocity on the other; and addition of smooth pursuit tests to the test battery. For further details of these modifications and the considerations which led to them, *see* the section 'Methodological Aspects' in the Discussion.

The horizontal position of the eyes was measured with the aid of nonpolarizable Beckman miniature silver-silver chloride (Ag-AgCl) skin electrodes placed on the inner and outer canthi of the eyes so as to permit separate recording for each eye. The signals from the electrodes were amplified to a level of about 1 V with a two-channel optically coupled and battery-powered (rechargeable) AC amplifier (gain 5×10^3; time constant 20 s). Eye positions could be determined to within about 1 deg after passing the signals through a 60 Hz (−3dB down) analog low-pass filter (roll-off: 12 dB/octave). Patients were seated in a darkened room and their vision was allowed to become adapted to the low level of illumination for 10 min before measurements were started. Head movements were prevented by a support at the back of the head. The complete measuring procedure lasts about 20 min, is not traumatic and is easy to perform both for the patient and the examiner. It does not cause any patient fatigue.

During the measuring procedure eye movement and stimulus signals were displayed on an oscilloscope screen and simultaneously recorded on magnetic tape (Bell and Howell CR 3000). Targets for saccades consisted of GaAs diodes emitting red light ($\lambda = 635$ nm) mounted in a cylindrical screen (radius 1 m) and subtending a visual angle of 0.25 deg each. Patients viewed the screen from a distance of 1 m. The target luminance was about 30 dB above the foveal threshold level. All saccade trials started from a 'primary position' in which the patient's gaze was directed towards the centre of the screen. A random target selector generated horizontal target steps of variable amplitude (10, 20 and 30 deg) to the left or right of the primary position.

Subjects were instructed to fixate the peripheral target spot presented for 2 s as quickly and accurately as possible. At the same time as the peripheral target was extinguished the central target was relit, evoking a saccade back to the primary position of gaze. Because of the predictable occurrence of the return saccade, data on it were not included in latency studies. The time between two succeeding stimuli was varied at random between 2 and 4 s, so that the patient was unaware precisely when or where the stimulus was going to occur. A complete saccade test consisted of 4 runs, each run comprising about 10 stimuli and lasting about a minute. A rest period of about 30 s was introduced between runs. With the aid of the diodes mounted in the cylindrical screen, a number of static perimetric measurements were also carried out in order to determine the presence of possible peripheral scotomas. The luminance of each diode was adjustable. In these measurements, the patient fixated the dim central diode while the intensity of a peripheral diode was slowly increased, and pressed a button at the moment when the peripheral target became visible. Detection thresholds determined in this way for a series of peripheral positions (10, 20 and 30 deg to the left and right of the central position) permitted the detection of possible peripheral scotomas. In less serious cases the eye movement data for these positions determined in the other experiments could be corrected, while the presence of more serious scotomas led to exclusion of the experimental results for the patient in question.

Horizontal smooth pursuit was elicited by a target moving in simple harmonic motion along a horizontal line through the fovea, provided by a laser beam ($\lambda = 630$ nm; output power 0.1 mW) reflected by a mirror galvanometer driven by a sine wave function generator on to a screen. The amplitude of the sine wave on the screen was about 12 deg. The stimulus frequency was initially 0.2 Hz, corresponding to a maximum velocity of 15 deg/s, and was increased in 0.2 Hz steps up to a value where pursuit was completely abolished and replaced by saccades. The frequency was then dropped by 0.1 Hz and decreased the same amplitude so that the negative-going frequency values were interleaved between the positive-going values. Each stimulus was presented for about 30 s. Rest periods of variable duration were introduced between successive runs.

Finally each patient was checked for nystagmus with the eyes open and closed in the primary position and with lateral gaze to both sides. Vertical ocular motility was studied by visual inspection of the eyes while the patient was looking up or down.

Parameters Studied

The saccadic latency and maximum saccadic velocity were determined quantitatively by measurements on eye movement recordings. The accuracy of saccadic eye movements and the presence of nystagmus was assessed by visual inspection of the recordings.

Normal subjects are able to follow a continuously moving target without noticeable saccadic interruption up to a velocity of about 30 to 35 deg/s. In our procedure this corresponds to stimulus frequencies of about 0.4 to 0.5 Hz. Below these frequencies, pursuit gain (maximum eye velocity/maximum stimulus velocity) is nearly unity. Interruption of pursuit by saccades may be due to a state of reduced alertness or by anticipation of the target's motion by a nervous patient (Gay *et al.*, 1974). To attribute pursuit abnormality to a pathological condition we strictly followed the rule that (symmetrical) pursuit should only be judged to be abnormal when the pursuit gain is below 0.5 at a stimulus frequency of 0.5 Hz. On the other hand, asymmetry of pursuit may be evident even at lower frequencies. Pursuit abnormalities at low stimulus frequencies (0.2 to 0.3 Hz) marked by regular interruption by small saccades are most probably due to cerebellar disorders.

Data Processing

Eye position, eye velocity and target position were fed *via* an analog-to-digital converter with a sample frequency of 500 Hz to a PDP 11/03 computer, where they were processed. Eye and target position were simultaneously recorded on an Elema Mingograf 81 with a paper speed of 50 mm/s. The recordings were used for visual checks on the data and if necessary for correction of computer results.

RESULTS

Saccadic Latency

Normative data were obtained from a group of 16 healthy subjects (mean age 33 years; range 19 to 56 years). The mean observed saccadic latency was 205 ms (standard deviation (SD) = 22 ms). Both these values agree with findings of other authors in normal subjects (Carpenter, 1977). Patient latency data were regarded as abnormal when the mean latency exceeded 270 ms (mean normal value plus 3 x SD). The observed latency data for our 84 MS and 21 ON patients are summarized in the normalized histograms of fig. 1.

Abnormal prolongation of saccadic latency was found in 80 per cent of the definite, 55 per cent of the probable and 24 per cent of the possible MS patients. In total, 49 of the 84 MS patients (58 per cent) showed abnormally high mean saccadic latency. Five of the ON patients (25 per cent) showed an abnormal mean saccadic reaction delay.

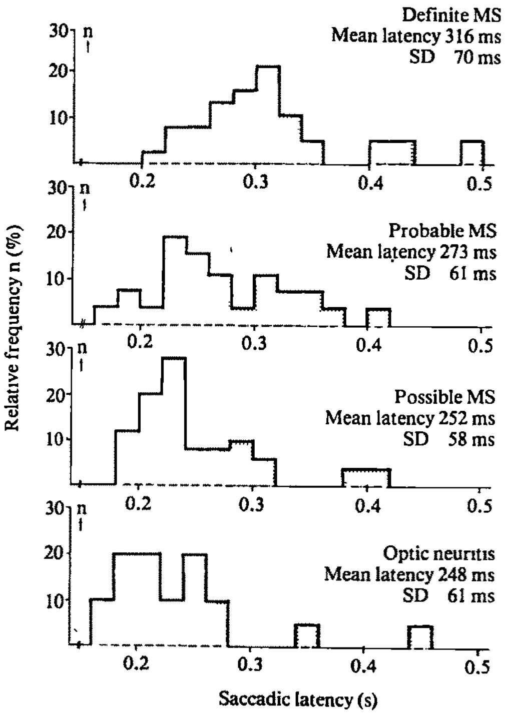
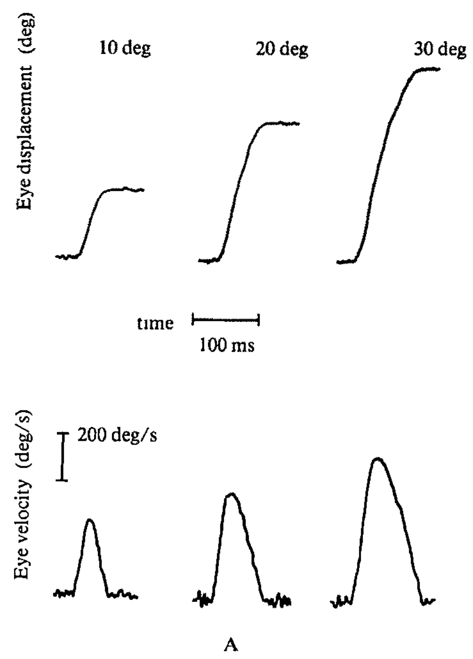
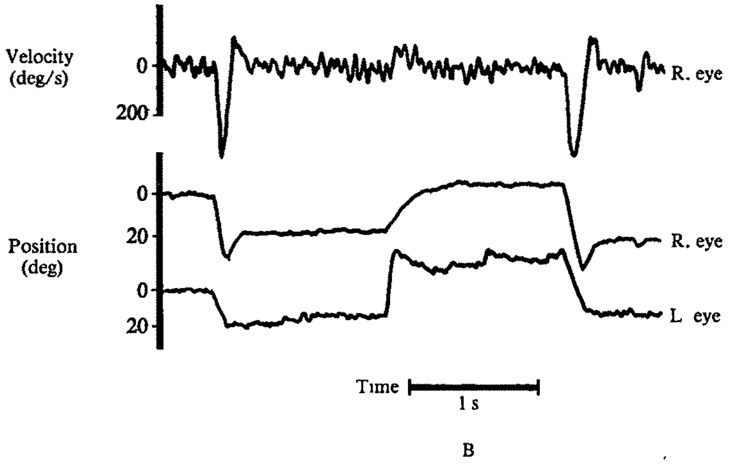


FIG. 1. Percentage distribution of mean saccadic latency for patients with definite, probable, and possible MS, and optic neuritis. The mean latency and standard deviation (SD) are indicated for each group. The shaded area indicates the proportion of patients with abnormally high mean saccadic latency (> 270 ms)

FIG. 2. Position and corresponding velocity recordings of normal and abnormal horizontal saccadic eye movements. A, displacement and velocity recordings of normal saccadic eye movements for three different amplitudes (10, 20 and 30 deg). B, eye movement recordings for a patient with bilateral internuclear ophthalmoplegia showing abduction overshoot and slowing of adduction. A modest dissociated nystagmus is sometimes present in the abducting eye. The upper curve represents the velocity of the right eye. Target displacement is 20 deg to the right.





Saccadic Velocity

Normal saccades with corresponding velocity signals are shown in fig. 2A for various saccade amplitudes. The saccadic velocity is regarded as abnormal when its maximum value is below the normal mean value minus 3 × SD. As can be seen from fig. 2A, the maximum saccadic velocity increases with increasing amplitude. As a result, normal velocity limits depend on the saccade amplitudes and are 220 deg/s for an amplitude of 10 deg, 300 deg/s for an amplitude of 20 deg and 400 deg/s for an amplitude of 30 deg.

Unilateral or bilateral slowing of adduction and abduction saccades, suggesting an ipsilateral and/or contralateral pontine tegmental lesion was detected in one definite MS patient. The velocity abnormality most frequently detected was internuclear ophthalmoplegia (INO), indicating a unilateral or bilateral lesion of the medial longitudinal fasciculus (MLF). While bilateral INO (fig. 2B) is a characteristic manifestation of MS, unilateral INO is also frequently detected among MS patients, as may be seen from Table 2.

A high incidence of INO (53 per cent) is found among clinically definite MS patients as compared with 17 per cent in the probable and 15 per cent in the possible group. One patient with symptoms of an optic neuritis showed a bilateral INO on oculomotor testing. This finding, combined with the observed presence of hemisphere hyperdense contrast enhanced areas on the CT scan, led to the patient being assigned to the definite MS group. MLF involvement was found subclinically in 16 of the 84 patients (9 bilateral, 7 unilateral). The number of subclinical INOs found among MS patients with an INO was high in all categories (definite 60 per cent; probable 60 per cent; possible 100 per cent). Unilateral INO was always found to be subclinical. The combined incidence of subclinical saccade velocity abnormalities is summarized in Table 2. The combined incidence of velocity abnormalities (19 per cent) is low despite the directed search for these disorders.

TABLE 2. INCIDENCE OF BILATERAL OR UNILATERAL INTERNUCLEAR OPHTHALMOPLEGIA (INO) IN THE DEFINITE, PROBABLE AND POSSIBLE MS GROUPS AND THE ON GROUP (THE NUMBERS BETWEEN BRACKETS REPRESENT SUBCLINICAL CASES) AND THE COMBINED PERCENTAGE OF SUBCLINICAL VELOCITY DEFICITS

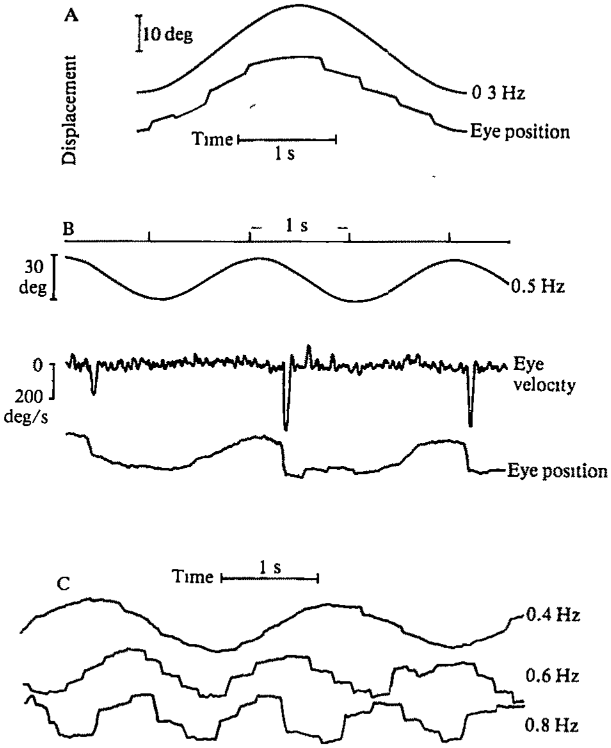
Clinical category	*Total No. of patients*	*No of patients with*		*Percentage of patients with subclinical velocity disorder*
		Bilateral INO	*Unilateral INO*	
Definite MS	28	11 (5)	4 (4)	33
Probable MS	30	5 (3)	— —	10
Possible MS	26	1 (1)	3 (3)	15
Total MS	84	17 (9)	7 (7)	19
ON	21	1 (1)	— —	5

Smooth Pursuit

Substitution of smooth pursuit by saccades (cogwheel pursuit as illustrated in fig. 3A) and asymmetry of pursuit (fig. 3B) are the most commonly detected patterns of smooth pursuit disorder. Both cause a drop in pursuit velocity gain with respect to normative data at higher stimulus frequencies.

Pursuit movements in response to three different stimulus frequencies are illustrated in fig. 3C. At 0.4 Hz, pursuit is practically uninterrupted by saccades while a slight increase in frequency to 0.6 Hz is enough to replace smooth pursuit nearly completely by saccades. The presence of small saccades at low stimulus frequencies

FIG 3.· Horizontal smooth pursuit eye movements in response to a sinusoidally moving stimulus of peak to peak amplitude 30 deg. A, cogwheel pursuit at 0.3 Hz (upper curve. stimulus) B, pursuit to the right almost completely substituted by saccades resulting in smooth pursuit asymmetry at 0.5 Hz (upper curve· stimulus). C, smooth pursuit movements at different stimulus frequencies. At 0.6 Hz pursuit is nearly completely saccadic.



(0.2 to 0.3 Hz) is most probably an indication of cerebellar involvement (fig. 3A). The incidence of abnormal pursuit eye movements decreases successively from the definite (76 per cent) through the probable (52 per cent) to the possible (28 per cent) categories of MS patients. The combined incidence of pursuit disorders is 52 per cent. Three ON patients (14 per cent) showed cogwheel pursuit abnormalities (Table 4).

Summing the various horizontal eye movement deficits, we found a high total percentage of abnormalities in MS and ON patients (Table 4). However, only 2 of the probable, 2 of the possible MS patients and 1 ON patient showed a pursuit deficit without any other disorder of the oculomotor system. The relatively small number of isolated smooth pursuit disorders would seem to indicate that the pursuit test is less valuable as a diagnostic tool than the saccade test.

The real merit of pursuit examinations in MS and ON patients is not really adequately reflected by the data of Table 4. It has been suggested that in the cerebral hemispheres the smooth pursuit system is anatomically separated and functionally different from the saccadic system and that cerebral lesions tend to affect each mechanism separately unless the lesion is very large or there are multiple lesions (Gay *et al.*, 1974). Such discrete defects are less common in those areas where the oculomotor pathways are close together. This holds especially for brainstem areas (paramedian pontine reticular formation, MLF, oculomotor nuclei), basal ganglia, superior colliculi and cerebellum. In particular, the occurrence of a pursuit disorder combined with another eye movement deficit may indicate multiple lesions in the region of the oculomotor system, thus increasing the reliability of a diagnosis based on deficits detected in the saccade test. This may be illustrated with the aid of two examples. First, saccadic dysmetria is thought to be caused by lesions of the cerebellar vermis (Selhorst *et al.*, 1976). Some patients with this complaint in a mild and subtle form show pursuit movements interrupted by small saccades. Saccadic disruption apparent at low stimulus frequencies (0.2 to 0.3 Hz) is suggestive of a lesion of the cerebellar flocculus. This finding thus supports the primary diagnosis of a cerebellar lesion. Secondly, pursuit asymmetry as a sign of multiple structure involvement indicates, although with little positional specificity, lesions of occipito-mesencephalic pathways contralateral to the direction of disturbed movements.

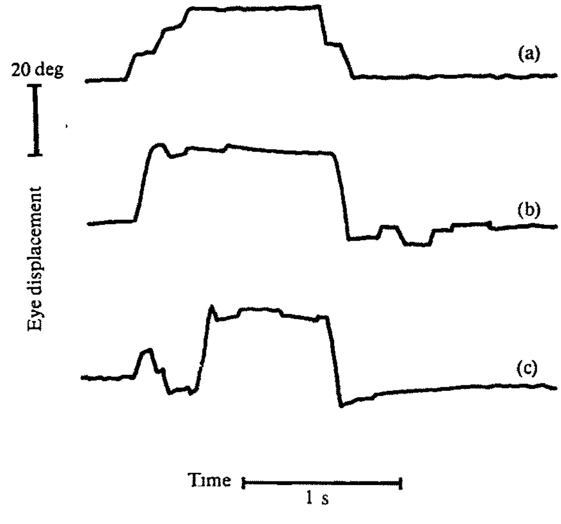


FIG 4 Eye movement recordings illustrating cerebellar disorders of saccade accuracy. (a) undershoot dysmetria, (b) overshoot dysmetria, (c) flutter dysmetria.

Other Oculomotor Disorders

Abnormalities of saccadic latency, saccadic velocity and smooth pursuit are frequently detected in MS patients. However, several patients show other eye movement disorders in addition to the above, or on their own. Among these, subclinical abnormalities involving the cerebellum such as saccadic undershoot or overshoot dysmetria (fig. 4(a), (b)), flutter dysmetria (fig. 4(c)), acquired pendular nystagmus and fixation instability (fig. 5), are relatively frequent. Our results show 9 definite, 7 probable and 4 possible MS patients with one or more of these eye movement defects thought to be caused by cerebellar lesions. Saccadic dysmetria

TABLE 3 INCIDENCE OF SUBCLINICAL OCULOMOTOR DISORDERS OTHER THAN SACCADIC LATENCY, SACCADIC VELOCITY OR SMOOTH PURSUIT DEFICITS AMONG THE THREE CATEGORIES OF MS PATIENTS

Oculomotor abnormality	*Definite MS* ($n = 28$)	*Probable MS* ($n = 30$)	*Possible MS* ($n = 26$)
Dysmetria	4	2	3
Flutter dysmetria	1	1	—
Fixation instability	5	6	3
Acquired pendular nystagmus	—	1	—
Gaze-evoked nystagmus	1	1	—
Vestibular disorder	—	2	4
Paresis of VIth cranial nerve	—	—	1

and fixation instability were most common (Table 3). Both disorders were found subclinically in 6 MS patients (2 from each category) at the time of examination. Nystagmus due to a vestibular imbalance measurable when the eyes are closed, and gaze-evoked nystagmus elicited in both eyes by attempted maintenance of eccentric eye positions (about 20 to 30 deg) were less common. Vestibular disturbance combined with saccadic dysmetria and fixation instability was found in 2 MS patients, suggesting (multiple) lesions in both the vestibular and cerebellar parts of the oculomotor system.

The results of the saccade test are judged to be abnormal when at least one of the three kinds of oculomotor deficits, listed in Table 4, is detected, namely, abnormally high mean saccadic latency, saccadic velocity disorder or one of the disorders shown in Table 3. It goes without saying that the combined incidence of saccadic abnormalities and even more so of saccadic plus pursuit deficits is higher than that of each disorder separately unless there is complete correlation between the incidence of the various complaints. This is true both for the total and the subclinical incidences among MS and ON patients in Table 4. In other words, by increasing the number of different conditions for which we screen, we increase the chance of detecting demyelination in different structures many of which do not show up at all on clinical examination.

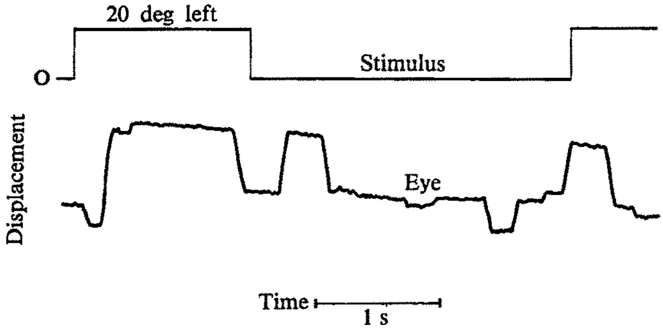


FIG. 5. Eye movement recordings showing fixation instability manifested as square wave jerks between successive stimuli.

TABLE 4. PERCENTAGE INCIDENCE OF SACCADIC AND PURSUIT DEFICITS AMONG THE VARIOUS CLINICAL SUBGROUPS THE LAST TWO COLUMNS GIVE THE PERCENTAGES OF OVERALL AND SUBCLINICAL OCULOMOTOR INVOLVEMENT DETECTED BY THE COMBINATION OF ALL TESTS

	Saccade test					*Pursuit test*	*Combined tests*	
Clinical category	*Latency*	*Velocity*	*Other disorder*	*Total*	*Subclinical total*	*Total*	*Total*	*Subclinical total*
Definite MS	80	56	30	85	80	76	85	80
Probable MS	55	17	33	77	67	52	77	74
Possible MS	24	15	32	52	52	28	60	60
Total MS	58	29	31	72	65	52	74	71
ON	15	5	—	20	20	14	25	25

Spinal Cord Involvement

As was mentioned in the Introduction, the diagnosis of MS must be based on evidence of the existence of at least two lesions in the white matter of the CNS (Schumacher *et al.*, 1965; McAlpine *et al.*, 1972) which differ with regard to both function and anatomy. Particularly in the older patient in whom spinal symptoms may be the only indication of MS, it is diagnostically important to search for a second lesion in CNS structures other than the spinal cord, such as the structures responsible for oculomotor function. In order to throw light on these questions, we carried out the above-mentioned battery of oculomotor tests on MS patients in whom screening tests had revealed spinal cord involvement. The results are summarized in Table 5. Subclinical lesions of the oculomotor system were found in 14 of the 27 MS patients (52 per cent) studied with a clinically suspected spinal cord lesion, confirming the multiple manifestation of demyelination in these patients.

Relation Between the Occurrence of Different Oculomotor Abnormalities

The fact that the combined incidence of saccadic and smooth pursuit abnormalities due to lesions located in different parts of the CNS summarized in Table 4 is greater than the individual oculomotor disorder detection rate among all categories of MS and ON patients, indicates that the incidences of the different oculomotor abnormalities among the patients are not completely correlated. On the other hand, the combined incidence should be maximal if there were no correlations at all between the occurrence of the various oculomotor deficits studies. In practice we

TABLE 5 INCIDENCE OF OVERALL AND SUBCLINICAL OCULOMOTOR DISORDERS AMONG MS PATIENTS WITH CLINICAL SYMPTOMS OF A SPINAL CORD LESION

		Overall disorder		*Subclinical disorder*	
Clinical category	*No. of patients*	*No.*	*%*	*No.*	*%*
Definite MS	16	13	81	7	44
Probable MS	9	7	78	5	56
Possible MS	2	2	100	2	100
Total	27	22	81	14	52

may expect some association between certain oculomotor parameters. One of the objectives of the present study was to study possible functional and anatomical associations between different oculomotor disorders.

Values of the saccadic latency may be regarded as measures of neural conduction times in the rather long and complicated pathways of the oculomotor system, and may be expected to be affected by lesions (demyelination) anywhere along the relevant central sensory or motor pathways located in the white matter. The primary sensory pathway of the oculomotor system is the optic nerve which relays information for the visual cortex. However, it seems doubtful whether all abnormalities of saccadic latency or smooth pursuit can be due to lesions of this pathway. In order to investigate this point, we monitored the conductive function of the optic nerve in both eyes in our group of patients by means of visual evoked response (VER) investigations based on the response to reversal of stimulus pattern and tested the association of prolonged saccadic latency with abnormally increased VER latency (P-100 peak). To this end, the results are presented in contingency tables as described by Spiegel (1961) (*see* Table 6(a)). Application of the Yates corrected χ^2 test (Spiegel, 1961) to the data of Table 6(a) leads to rejection of the hypothesis that abnormally increased VER latency and abnormally increased mean saccadic latency are associated. This agrees with the findings of Ochs *et al.* (1978) and indicates clearly that lesions beyond the primary visual pathway contribute considerably to prolonged saccadic latency in both MS and ON patients.

TABLE 6 CONTINGENCY TABLES SHOWING DEGREE OF ASSOCIATION BETWEEN DIFFERENT OCULOMOTOR DISORDERS AND VER LATENCY (P-100 PEAK) DISORDER (+ = ABNORMAL, − = NORMAL). THE NUMBERS IN THE TABLES REFER TO ALL MS PATIENTS. (a) SACCADIC LATENCY *vs* VER LATENCY, (b) SMOOTH PURSUIT *vs* VER LATENCY, (c) SACCADIC LATENCY *vs* INO, (d) SMOOTH PURSUIT *vs* SACCADIC LATENCY AND (e) SACCADIC LATENCY *vs* CEREBELLAR INVOLVEMENT

	Latency	
	+	-
VER +	27	12
VER -	29	23

$\chi^2 = 1.2$ n.s.

(a)

	Pursuit	
	+	-
VER +	23	20
VER -	15	15

$\chi^2 = 0.003$ n.s.

(b)

	Latency	
	+	-
INO +	18	4
INO -	27	28

$\chi^2 = 5.65$ $P < 0.025$

(c)

	Pursuit	
	+	-
Latency +	35	9
Latency -	10	22

$\chi^2 = 15.9$ $P < 0.005$

(d)

	Latency	
	+	-
CER +	10	7
CER -	28	31

$\chi^2 = 0.3$ n.s.

(e)

CER = cerebellar disorder, n.s = not significant. The values of P given below the tables indicate the significance of the association found

The saccadic and pursuit systems have quite different functions, the former compensating for positional errors and the latter for velocity discrepancies between stimulus and eye. The corresponding anatomical pathways are also separated in the cerebral hemispheres (Gay *et al.*, 1974), although the optic nerves constitute the primary part of both. No statistically significant correlation is found between VER and pursuit abnormalities (Table 6(b)). On the other hand, quite a strong association is found between smooth pursuit disorder and abnormally high mean saccadic latency in MS patients (Table 6(d)).

Normal latencies for horizontal saccades have been reported in 4 patients with internuclear involvement (Baloh *et al.*, 1978). Results from MS and ON patients suffering from INO in our study reveal that the occurrence of INO is strongly correlated with an abnormal rise in mean saccadic latency (Table 6(c)). Except for one patient, definite MS patients, including the sole ON patient showing INO (n = 12, mean latency 323 ms), all showed increased mean saccadic latency. Probable MS patients showing INO (n = 5, mean latency 329 ms) all showed increased mean latency. Of the 4 possible MS patients with INO (mean latency 243 ms), only one showed abnormally high mean saccadic latency. Unlike MLF lesions, cerebellar lesions are not correlated with latency abnormality (Table 6(e)), nor is any association found between pursuit disorders and the presence of INO.

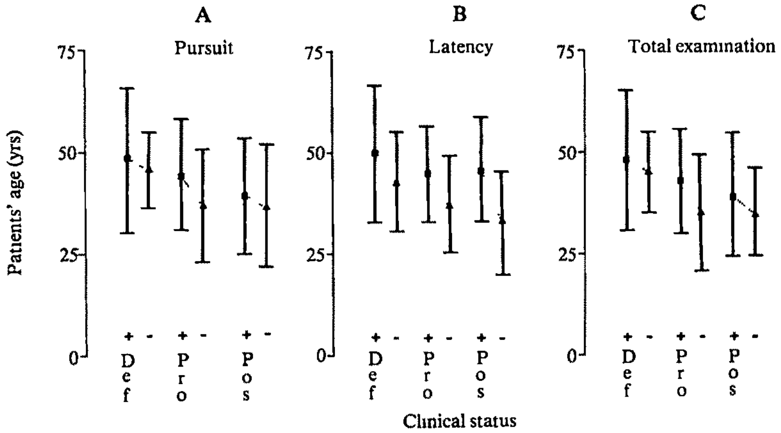


FIG. 6. Age range of definite (Def), probable (Pro) and possible (Pos) MS patients with (+) or without (−) latency, pursuit or overall oculomotor disorder. ■ = mean age of (+)group, ▲ = mean age of (−)group. The length of the vertical bars indicates the SD.

An effect of ageing on smooth pursuit performance has been reported in normal subjects (Sharpe and Sylvester, 1978). In our study, the group of normal controls did not show such an effect. The mean age of patients with pursuit disorders was slightly higher than that of those with normal pursuit performance (fig. 6A), but the difference was not statistically significant. A similar age trend is observed for saccadic latency abnormalities (fig. 6B).

Patients with oculomotor dysfunction tend to have a slightly higher mean age than those with normal oculomotor functions in all MS categories. This difference, however, is not statistically significant either. A similar relation is observed between saccadic latency (fig. 7A), smooth pursuit (fig. 7B) and overall oculomotor abnormality (fig. 7C) on the one hand and disease duration on the other. Patients without the above-mentioned disorders tend to have a slightly shorter history of MS, but the difference is not statistically significant.

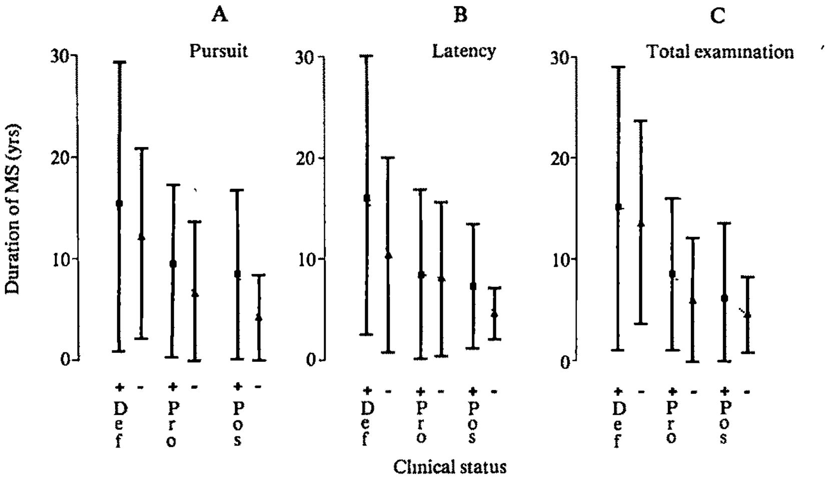


FIG 7. Spread of disease duration in definite (Def), probable (Pro) and possible (Pos) MS patients with (+) or without (−) latency, pursuit or overall oculomotor disorder. ■ = mean duration for (+)group, ▲ = mean duration for (−)group. The length of the vertical bars indicates the SD.

Optic Neuritis

Five ON patients (25 per cent) showed clear subclinical eye movement disorders (Table 4). The ON patients with oculomotor dysfunction were significantly younger (mean age 20 years) than those who did not (mean age 32 years). This difference was not found among MS patients. While the population of ON patients is too small (n = 21) to permit the drawing of definite conclusions, it appears that oculomotor dysfunction is predominantly present among the younger patients who are in the acute stage of the disease. Five of our ON patients were younger than 20 years (11, 12, 14, 15 and 19 years). The eldest was free of oculomotor abnormalities while the 15-year-old girl manifested a rather doubtful rise in saccadic latency (mean 265 ms; SD = 34 ms). The remaining 3 young patients all clearly showed oculomotor dysfunction. The presence of disorders is not correlated with the duration of ON complaints before eye movement examination.

As for the MS patients, we found convincing evidence that in cases of unilateral ON, normal (P-100 peak) VER latencies in the unaffected eye can be associated with abnormally high mean saccadic latencies. The most striking example of this was a female ON patient (aged 15 years) with normal VER responses and normal acuity of the sound eye, who showed a mean saccadic delay of 455 ms (SD = 100 ms).

DISCUSSION

Methodological Aspects

The findings of subclinical disorders of the medial longitudinal fasciculus (MLF) in 19 per cent of our MS patients (*see* Table 2) contrasts with the results of Tackmann *et al.* (1980), who found no evidence of internuclear ophthalmoplegia

(INO) in 55 patients. This difference is hardly surprising as Tackmann *et al.* (1980) used electrodes only at the outer canthus of both eyes for the recording of eye movements, thus measuring some average movement of the eyes. Kirkham and Katsarkas (1977) showed that the resulting saccade trajectory may not appear abnormal despite the presence of INO. Reliable detection of subclinical INO requires the recording of the movement of each eye separately by electrodes placed at the inner and outer canthi of both eyes. We therefore adopted this approach in our experiments.

Bilateral INO, eventually associated with vertical nystagmus in up and/or down gaze, is found most frequently in MS patients but is not pathognomonic for MS as there is an appreciable incidence in vascular disease (Gonyea, 1974); unilateral INO in older patients is merely an indication of infarction due to vascular disease in the brainstem (Cogan, 1970). Unilateral INO in relatively young patients, on the other hand, may indicate lesions of nonvascular origin (Cogan, 1970). Seven of 24 INOs (29 per cent) in our MS patients showed unilateral INO. It has been suggested that the mean age of unilateral INO patients is lower than that of patients suffering from bilateral INO (Cogan, 1970). In our MS and ON patient group, however, no statistically significant difference was found between the mean ages of unilateral INO patients (n = 7; mean age 50 years; SD = 14 years) and bilateral INO patients (n = 18; mean age 47 years; SD = 15 years). On the other hand, we found the mean duration of the disease to be lower for unilateral INO patients (n = 7; mean duration 7.9 years; SD = 3.8 years) than for bilateral (n = 18; mean duration 14.3 years; SD = 11.5 years). Student's t-test showed this difference to be barely significant at the $P < 0.1$ level.

It would therefore seem worth while undertaking follow-up studies to establish whether unilateral INO patients develop bilateral lesions.

Stimulus Presentation

Doubt must be cast on the results of studies of saccadic latency in which stimulus amplitude and timing are predictable (such as that by Mastaglia *et al.*, 1979). Unpredictable target presentation avoids anticipatory responses in the test subject. For this reason we induced saccades by a randomly presented stimulus with multiple choice of amplitude.

Most previous clinical studies of smooth pursuit have been performed with a pendulum, so that the stimulus frequency was determined by the length of the pendulum cord. Limitations imposed by the physical dimensions of most laboratories lead to a maximum stimulus frequency of about 0.3 Hz. However, our study confirms the suggestion by Solingen *et al.* (1977) that a pursuit deficit often only becomes manifest at higher stimulus velocities (*see*, for example, fig. 3C). The electronic equipment we used had the advantage of permitting smooth pursuit investigations at different stimulus frequencies. It should be noted that cogwheel pursuit due to cerebellar dysfunction normally appears at quite low stimulus velocities (this is also illustrated in fig. 3A).

Oculomotor Dysfunction and Severity of MS

A few authors have studied various eye movements among various categories of MS patients (Solingen *et al.*, 1977; Mastaglia *et al.*, 1979; Tackmann *et al.*, 1980). Such studies are particularly important aids in the diagnosis of patients without clinically apparent eye movement disorders. Solingen *et al.* (1977) found 13 of the 16 definite MS patients they studied to have eye movement disturbances on the basis of oculomotor measurements. They did not mention how many of this rather small group of patients showed clinical signs of oculomotor disorder. Tackmann *et al.* (1980) studied quite a large group (n = 55) of patients which they divided on the basis of criteria proposed by McDonald and Halliday (1977) into those with definite (n = 23), probable (n = 4), and suspected (n = 9) MS, together with a group (n = 9) with signs of paraplegia. Eighteen definite (78 per cent), 3 probable (75 per cent), 3 suspected (33 per cent) MS patients and 5 paraplegics (56 per cent) showed oculomotor disorders. These authors also gave no information as to the number of clinically apparent abnormalities.

TABLE 7 PERCENTAGE INCIDENCE OF EYE MOVEMENT DISORDERS AMONG COMPARABLE CATEGORIES OF MS PATIENTS WITH CLINICALLY NORMAL EYE MOVEMENTS AS DETERMINED IN THE PRESENT INVESTIGATION (REULEN *ET AL.*, 1983) AND BY MASTAGLIA *ET AL* (1979)

	Saccade test				*Pursuit test*				*Combined tests*			
Authors	*Def.*	*Prob.*	*Pos.*	*Total*	*Def.*	*Prob.*	*Pos.*	*Total*	*Def.*	*Prob.*	*Pos.*	*Total*
Mastaglia *et al.* (1979)	46	45	75	48	60	61	67	61	76	66	100	72
Reulen *et al.* (1983)	80	67	52	65	65	52	28	47	80	74	60	71

Data on patients with clinically normal eye movements from a study by Mastaglia *et al.* (1979) are presented in Table 7 in combination with our own data. While the number of patients in our study was almost double that of Mastaglia *et al.* (1979), the same rate of oculomotor disorder was found on the basis of the combined test results in the two series (71 and 72 per cent, respectively). These data substantially support the value of ocular diagnostic studies in MS patients. The saccade test revealed more abnormalities in our study (65 per cent) than in that of Mastaglia *et al.* (1979) (48 per cent).

According to Mastaglia *et al.* (1979), the study of reaction times and accuracy is more sensitive than the study of velocity in detecting saccade deficits. On the other hand, we found an almost equal incidence of velocity (29 per cent) and accuracy (31 per cent) disorders. The combination of different types of test results in the highest screening effectiveness for the detection of oculomotor abnormalities. The lower incidence of smooth pursuit deficits in our study (47 per cent as compared with 61 per cent for Mastaglia *et al.* (1979)) is more or less complemented by the saccadic test results (65 per cent as compared with 48 per cent). The lower smooth pursuit defect score found in our study may be due to a more stringent definition of pathological pursuit disorder. Although the combination of saccade and pursuit test results in our study does not greatly increase the rate of deficit detection (Table 4), the importance of smooth pursuit testing should not be underestimated. The major contributions it can make are the confirmation of a diagnosis already suspected on the basis of saccade test results and the detection of lesions in parts of the oculomotor system not involved in saccadic function.

Functional and/or Anatomical Mechanisms

The lack of correlation between increased VER latency on the one hand and abnormal mean saccadic latency and smooth pursuit abnormalities on the other supports the conclusion of Ochs *et al.* (1978) that lesions beyond the primary visual pathway substantially contribute to prolonged saccadic latency. This is not surprising, since most MS and ON patients suffer from monocular optic neuritis. In normal subjects, there is no difference between binocularly and monocularly evoked eye movements. We will explain this with reference to the simplified block diagram of the oculomotor system shown in fig. 8.

With regard to anatomy and function, the saccadic and smooth pursuit systems act in parallel between the visual and motor pathways. Fig. 8 shows that an isolated monocular ON does not interfere with proper functioning of either system, since the stimulus mediated by the unaffected eye will provide the afferent signal for the oculomotor system. No statistically significant correlation is found between binocularly delayed VER signals and saccadic latency in MS and ON patients with binocular ON. In our study, 7 patients with binocular ON and prolonged VER latencies in both eyes show normal mean saccadic latencies, while 6 patients with binocular ON and abnormal VER latencies in both eyes showed abnormally high mean saccadic latencies.

Internuclear ophthalmoplegia is regarded as a lesion of the motor pathways of the oculomotor system (*see* fig. 8). A significant correlation is found between INO and abnormally high saccadic latency among the definite and probable MS patients

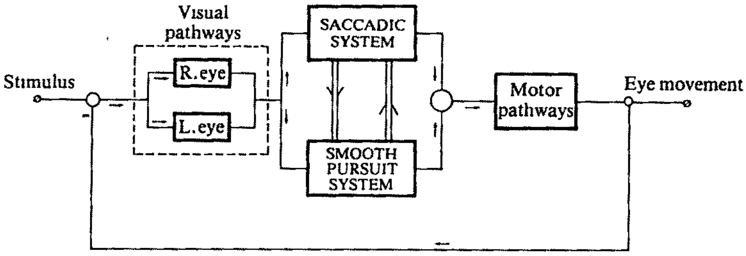


FIG. 8. Suggested functional block diagram of the oculomotor system showing afferent (visual) and efferent (motor) pathways. The interactions between the saccadic and the pursuit systems are indicated by arrows (⇒), and the direction of neural signal flow along the various pathways by small arrows (→).

(Table 6(c)). No association, however, is found between pursuit and INO abnormality. This finding agrees with our assumption that the saccadic and smooth pursuit systems act in parallel. Both in monkey and in man no report has been made concerning the association of abnormally high saccadic latencies and lesions exclusively restricted to one or both MLF causing unilateral or bilateral INO. The findings of an association between the occurrence of INO and latency disorders among our MS patients suggests that the process of demyelination may not be restricted exclusively to one or both MLF but may extend to other (brainstem) structures functionally involved in the triggering of saccades. Studies in primates reveal that lesions of one or both superior colliculi cause a substantial rise in saccadic latency (Wurtz and Albano, 1980). High saccadic latencies are also found in about 70 per cent of patients suffering from Parkinson's disease and are attributed to lesions of the basal ganglia (Teräväinen and Calne, 1980).

Smooth pursuit disorder is clearly correlated with abnormally high mean saccadic reaction times. The mutual interaction between the saccadic and smooth pursuit systems is likely to become manifest when the positional error increases during compensation of a velocity error between stimulus and eye by the pursuit system. At some moment, a decision is made to evoke a saccade to keep the fovea locked on to the stimulus, that is, to eliminate the existing positional error. Now there will be a certain delay between the decision to evoke a saccade and the subsequent execution of this saccade. This delay (or at least part of it) is due to the latency of the saccadic system. Provided no other pursuit deficits are present, an increase in saccadic delay may be expected to cause less efficient compensation of position error, so that pursuit movements may be excessively interrupted by saccades. This reasoning may provide a basis for explanation of possible associations between abnormally high saccadic latency and smooth pursuit disorder.

CONCLUSIONS

In this paper the value of standardized eye movement examination has been studied and discussed in relation to diagnostic considerations. The electrophysiological technique used takes little time and is easy to perform; it is not uncomfortable for the patient, and is quite sensitive. Hence it appears particularly suitable for repeated application for objective monitoring of the course of diseases of the CNS. The technique of objective examination of eye movements as described and evaluated in the paper provides a valuable tool for the diagnosis of MS.

As mentioned in the Introduction, ON patients were included in the study since ON is a threshold symptom in approximately 30 per cent of patients who later develop MS. Five of our 21 ON patients showed subclinical eye movement disorders. At present there is no firm evidence that ON as part of MS differs pathologically from ON occurring in isolation, or that the presence of an oculomotor disorder increases the risk of developing MS in the future.

ACKNOWLEDGEMENTS

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NEUROPSYCHOLOGICAL DEFICITS ASSOCIATED WITH SMALL UNILATERAL THALAMIC LESIONS

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SUMMARY

Neuropsychological deficits resulting from small, well demarcated, unilateral thalamic lesions were investigated in 13 right-handed patients. Fourteen patients with deep white matter lesions and 12 normal subjects served as controls. The performance of thalamic patients was generally worse than that of normals and patients with white matter lesions, although the lesions in the latter were significantly larger. There was no clear indication of a dichotomous lateralization of function at the level of the thalamus, although patients with left-sided lesions performed less well in almost all tests. There was some evidence of a rostrocaudal dichotomy, rostral thalamic lesions leading to memory deficits and caudal lesions to impairments of 'abstraction' and 'categorization'.

INTRODUCTION

The multiplicity of thalamic symptoms corresponds to the anatomical and functional heterogeneity of the thalamus. Thalamic pain, sensory disturbances, disturbances of the body schema, anosognosia, disorders of movement and posture, disturbances of consciousness, dementia, amnesic syndromes and affective and psychotic disorders have all been described with thalamic lesions in humans (reviewed by Martin, 1968).

The diagnosis of thalamic lesions has been facilitated by the introduction of CT scanning and, accordingly, the number of patients with such lesions investigated by neuropsychological methods has greatly increased. In a number of cases language disturbances have been described from posterior thalamic lesions in the dominant hemisphere, mostly in the acute stage after a cerebral haemorrhage (for example, *see* Fisher, 1959; Ciemins, 1970; Mohr *et al.*, 1975; Reynolds *et al.*, 1979; Cappa and Vignolo, 1979; Alexander and LoVerme, 1980). Other evidence for the participation of thalamic nuclei in language function comes from stereotaxic operations and stimulation (for example, *see* Allan *et al.*, 1966; Ojemann *et al.*, 1968; Darley *et al.*, 1975).

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Reports on neuropsychological deficits other than language disturbances resulting from thalamic lesions are scarce. 'Thalamic dementia' following bilateral lesions has been described in a number of instances (Schuster, 1936; von Grünthal, 1942; Castaigne *et al.*, 1966; Chassagnon *et al.*, 1969; von Cramon *et al.*, 1981). This type of dementia is reported to be similar to frontal lobe syndromes (von Grünthal, 1942) with the accent on an impairment of 'social intelligence' (von Cramon *et al.*, 1981). Riklan and Levita (1969) described transient intellectual deficits resulting from stereotaxic thalamotomy but could not demonstrate lasting disturbances. An amnesic syndrome has also been described with bilateral anterior thalamic lesions (von Cramon and Eilert, 1979; Schott *et al.*, 1980), and degenerative changes in the anterior thalamus have been found in patients with Korsakov's syndrome (Victor *et al.*, 1971).

In thalamic dementia as well as in the few cases of amnesic syndromes, the lesions were bilateral and symmetrical. Whereas language alterations seem to occur only with left thalamic lesions, right thalamic lesions have been found to interfere with visual pattern perception and recognition (Ojemann, 1977; Vilkki, 1978).

This investigation reports cognitive changes in a group of patients with unilateral circumscribed thalamic lesions. Language disturbances are not included, as they will be reported elsewhere (Wallesch *et al.* (1983). In preparation). The main purpose of this study was to discover whether small unilateral lesions of the thalamus lead to disturbances of cognitive function.

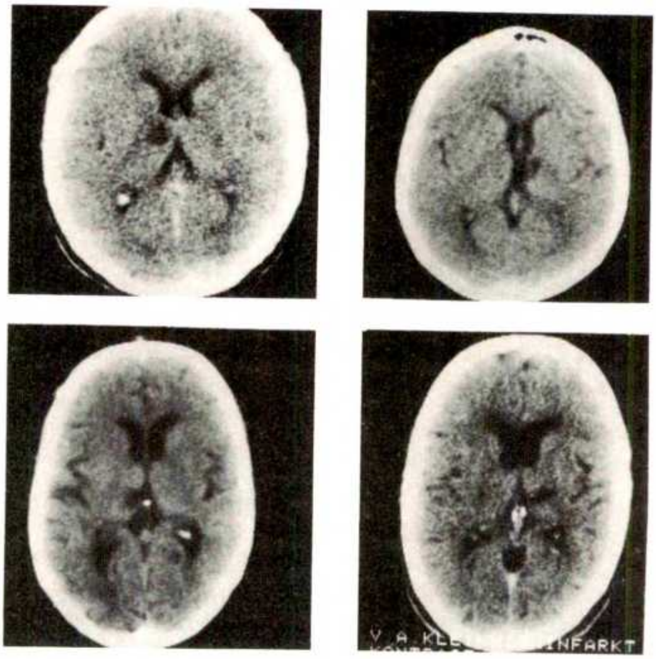

FIG. 1. CT scans of 4 patients with thalamic lesions.

PATIENTS

Thirteen patients with circumscribed thalamic lesions (8 ischaemic, 5 haemorrhagic; 6 left, 7 right) and 14 patients with small ischaemic lesions in the deep white matter of the cerebral hemispheres (8 left, 6 right) were investigated. The lesions were verified by CT scans on a 256 × 256 pixel matrix. Fig. 1 shows the CT scans of 4 patients with thalamic lesions in the chronic phase. Patients with cerebral atrophy, multiple lesions or lesions that involved cortex or basal ganglia were not included. All patients were native right-handed Germans. Details of the patients are shown in Table 1. The diagnosis was confirmed in 26 patients by CT scans in the acute stage. In one patient (A.G.) the diagnosis was made on clinical grounds and confirmed later by a CT scan.

An interval of six months to twelve years without a further cerebral accident elapsed before testing. The control group consisted of 12 subjects, comprised of patients with lumbar disc prolapse, visitors to the hospital and nonacademic staff. They were matched with both patient groups by age, years of schooling and social class.

TABLE 1. CLINICAL DATA FOR PATIENTS WITH SMALL UNILATERAL THALAMIC AND WHITE MATTER LESIONS

Patient	*Sex*	*Age (yrs)*	*Type of pathology*	*Site of lesion*	*Symptoms at time of investigation*	*IQ*
Left thalamic lesions						
S.F.	F	69	Ischaemia	Rostral	Minimal R hemiparesis, hypaesthesia R leg	87
E.C.	M	59	Haemorrhage	Caudal	None	92
H.P	M	57	Ischaemia	Rostral	None	111
K.K.	F	69	Ischaemia	Medial	Frontal headaches	99
E.M.	M	59	Haemorrhage	Caudal	Minimal R hemiparesis, R. homonymous visual field defect	76
A.K.	M	60	Haemorrhage	Caudal	Minimal dysarthria, R. homonymous visual field defect	90
Right thalamic lesions						
O.W.	M	65	Ischaemia	Caudal	Minimal L. hemiparesis	93
J.Sch.	M	44	Ischaemia	Rostral	Moderate L. hemiparesis, L. hemihypaesthesia	83
W.A	M	61	Ischaemia	Rostral	None	95
M M.	F	71	Ischaemia	Medial	None	102
A.G	F	67	Haemorrhage	Medial	Paresis, dystonia, and paraesthesiae in L arm	100
R L	F	47	Ischaemia	Rostral	None	85
G.F.	F	56	Haemorrhage	Caudal	L. homonymous visual field defect	110
Left white matter lesions						
G O.	M	42	Ischaemia	Int. caps.	Moderate R hemiparesis	102
E.P	F	55	Ischaemia	Frontal	Increased R. arm reflexes	94
H L.	M	57	Ischaemia	Temporal	R. leg paresis	105
M.Sch.	F	57	Ischaemia	Temporal	Increased R. arm reflexes	104
K.M.	M	58	Ischaemia	Temporal	None	111
J.T.	M	64	Ischaemia	Frontal	R. arm reflexes	81
C F.	M	66	Ischaemia	Insular	Minimal R. brachiofacial paresis	93
E.B.	F	67	Ischaemia	Insular	None	109
Right white matter lesions						
P.S.	M	57	Ischaemia	Int. caps.	Minimal paresis left arm	90
I.H	F	57	Ischaemia	Parietal	L. homonymous visual field defect	98
R.H.	M	59	Ischaemia	Int. caps	None	94
E E	F	60	Ischaemia	Parietal	Increased L. arm reflexes	104
A.R.	M	61	Ischaemia	Frontal	Increased L arm reflexes	96
M.G.	F	66	Ischaemia	Parietal	None	94

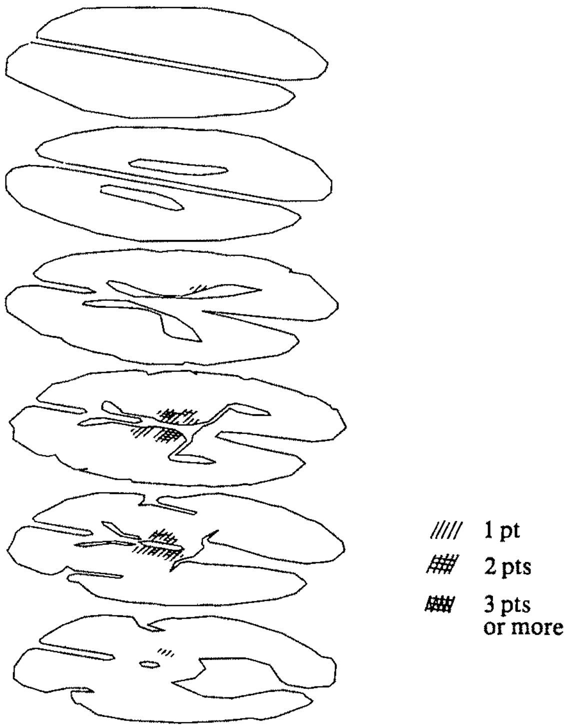

FIG. 2. Compound plot of the CT scan lesions in 13 patients with unilateral thalamic lesions

The CT scans of both patient groups were evaluated by the method of Blunk *et al.* (1981), which was extended to include high frontoparietal slices. This method requires transcription of the defects as shown by the CT scan to standard matrices. By counting the number of matrix pixels included by a lesion over all slices, a rough estimate of the volume of the lesion as a percentage of hemisphere volume can be obtained. This method is not very accurate for small lesions, as the partial volume effect can only be estimated. Fig. 2 shows a superimposed plot of the thalamic lesions and fig. 3 the white matter lesions.

METHODS AND MATERIALS

The informed consent of the subjects was obtained. They were tested in one or two sessions in the Neuropsychological Laboratory of the Department of Neurology, Ulm University, or in a quiet room at their homes. Assessment was discontinued if any sign of fatigue occurred.

The following tests were used. (1) Digit Span, Arithmetic, Similarities, Picture Arrangement and Block Design of the German version of the Wechsler Adult Intelligence Scale (HAWIE, Wechsler *et al.*, 1964). (2) Benton Visual Retention test (Benton, 1972, German version), form E, 10 s exposure of figures, no delay. (3) Standard Progressive Matrices, sets A to C (Raven, 1956). (4) Wisconsin Card Sorting test (Grant and Berg, 1948). A simplified evaluation was used, in which only the number of criteria achieved and the number of correct responses were considered. One hundred and

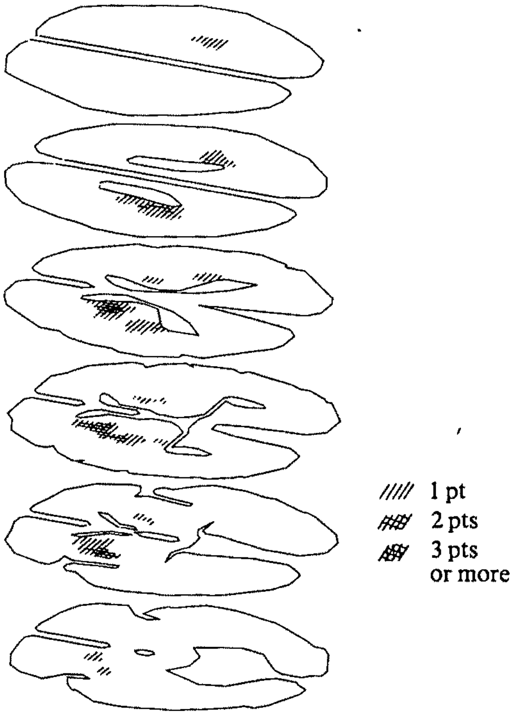

FIG. 3. Compound plot of the CT scan lesions in 14 patients with unilateral deep white matter lesions.

twenty-four cards were given in random order. If the subject achieved 6 sorting criteria (colour, form, number) with a smaller number of cards, the test was discontinued and the number of correct responses was extrapolated. (5) Sequential Concept Formation (Talland, 1965). The subjects were asked to learn and finally predict the sequence of colours of an ordinary pack of playing cards, sorted in the sequence Red/Red/Black/Black/Red/Black/R/R/B/B/R/B . . . They were instructed that the cards were sorted in a certain repetitive sequence of colours, that they had to guess the colour of the next card at the beginning and learn the sequence simultaneously in order to be able to predict correctly from memory. The number of correct responses in the first 72 trials was counted.

We assumed that the WAIS/HAWIE and the Progressive Matrices would serve as measurements of deficits of intelligence and Digit Span, and the Benton test as a test of immediate recall, the Sequential Concept Formation as a test of learning and retaining within a range of minutes with distraction, and the Similarities and the Wisconsin Card Sorting tests as measurements of concept formation and abstraction abilities (Goldstein, 1944; Milner, 1963).

The results were analysed by the U-test of Mann and Whitney (Siegel, 1956). As the size of lesion in the patient groups differed significantly, only two-sample comparisons were undertaken. In the context of the study, the U-test cannot be regarded as a test of 'significance' in the strict sense, as we investigated a large number of variables with limited numbers of patients. The comparisons were not independent. The P values given in the Tables are thus only comparative measurements of the relative size of differences.

RESULTS

The performance of patients with thalamic lesions was inferior to that of normal controls in all measurements, and to that of patients with white matter lesions in almost all tests, although lesions in the latter group were significantly larger (Table 2). Conspicuous differences between the patient groups which, except for the Similarities test, did not reach the 5 per cent level of probability occurred with the Similarities, Arithmetic, Block Design, Wisconsin Card Sorting and Sequential Concept Formation tests. The performance of patients with white matter lesions did not differ significantly from the controls.

As these results could be explained by nonspecific effects such as dementia or motivational disturbances, there is no indication of a specific cognitive deficit resulting from all thalamic lesions.

Left-Right Comparisons

The performance of patients with left thalamic lesions was worse than with right-sided lesions in all measurements (Table 3). In most instances the differences

TABLE 2 COMPARISON OF NEUROPSYCHOLOGICAL TEST RESULTS FOR PATIENTS WITH UNILATERAL THALAMIC AND WHITE MATTER LESIONS AND CONTROLS

	Controls			*Thalamic lesions*			*White matter lesions*	
	$\bar{X}$	*SD*		$\bar{X}$	*SD*		$\bar{X}$	*SD*
n	12			13			14	
Lesion size*	0			0.26	0.12	⟺	0.58	0.34
Age	58.3	10.2		60.3	8.2		59.0	6.3
Full scale IQ	106.7	9.7	⟺	94.1	10.3		98.2	8.1
Verbal IQ	107.5	7.9	⟷	97.5	8.5		102.2	7.9
Performance IQ	106.2	12.9	⟺	90.6	11.9		94.6	9.3
Digit Span	9.8	1.8		9.0	2.2		8.9	2.7
Arithmetic	9.3	2.3	⟷	7.3	1.8		8.6	2.1
Similarities	10.3	1.7	⟺	8.2	2.1	⟷	9.6	1.4
Picture Arrangement	10.0	3.1	⟷	7.0	2.3		7.0	2.0
Block Design	9.0	2.3	⟷	6.4	2.0		7.6	2.8
Benton test								
Correct	5.7	2.3	⟷	3.2	1.7		4.4	1.9
Errors	6.9	3.8	⟷	11.2	4.0		9.1	3.1
Progressive Matrices	23.9	5.2		19.1	5.7		20.1	4.5
WCS								
Correct	82.5	14.6	⟷	66.4	11.1		75.6	18.1
Criteria	4.5	1.8		3.5	1.5		4.0	1.4
SCF								
Correct	55.3	9.6	⟷	46.0	7.3		53.6	9.6

* Percentage of hemisphere volume Arrows indicate U-test probabilities of less than 5 per cent, double arrows of less than 1 per cent. WCS = Wisconsin Card Sorting test. SCF = Sequential Concept Formation.

were rather small and can be disregarded, the only difference to reach the 5 per cent level being found with the Benton test. There is no indication of a dichotomous lateralization at thalamic level, with verbal functions lateralized to the left and visuoconstructive and/or visuoperceptive to the right. In comparison with patients with left-sided white matter lesions who, probably by chance, were the best overall performers of all the patient groups in this study, left thalamic patients scored worse in the Benton test and the Sequential Concept Formation, and above the 5 per cent level for IQ, Arithmetic, Similarities, Block Design, Progressive Matrices and Wisconsin Card Sorting.

The results of the comparison by laterality again are in favour of rather nonspecific cognitive effects of thalamic lesions.

Rostral–Caudal Comparisons

The anatomical inhomogeneity of the thalamus, with more than 30 distinguishable nuclei, suggests localizing principles of cognitive function other than lateralization. The resolution of the CT scan at present is not sufficient to decide which thalamic nuclei are damaged, except perhaps for the pulvinar. Moreover, functional abnormalities at the margins of the lesions demonstrated in the scans have to be considered. What is possible, however, is to state whether a lesion is located in anterior (or rostral) or posterior (or caudal) thalamus.

TABLE 3 COMPARISON OF NEUROPSYCHOLOGICAL TEST RESULTS WITH LEFT AND RIGHT THALAMIC AND WHITE MATTER LESIONS

	Left-sided lesions						*Right-sided lesions*			
	White matter			*Thalamus*			*Thalamus*		*White matter*	
	X̄	*SD*		*X̄*	*SD*		*X̄*	*SD*	*X̄*	*SD*
n	8			6			7		6	
Lesion size	0.66	0 36	⟷	0.26	0.12		0.24	0.12	0.48	0.30
Age	58.3	8.0		62 0	5.5		58.9	10.2	59.7	3.2
Full scale IQ	100.6	8.4		92.5	11.8		95.4	9 5	96.0	4.7
Verbal IQ	102.6	9.4		95.8	8.6		98.9	8.8	101.7	6.1
Performance IQ	98.4	9.6		89.3	13.9		91.7	10.8	89.5	6.3
Digit Span	8.8	3.1		8.5	2.3		9.4	2.2	9 2	2.3
Arithmetic	9.0	2.1		6.8	1.3		7.7	2.1	8.0	2.2
Similarities	9.8	1 6		7.8	2.8		8.4	1 4	9.3	1.2
Picture Arrangement	7.2	2 1		6.8	2.2		7.1	2.5	6.6	1 9
Block Design	8.6	2.9		5.7	2.7		6 9	1 3	6 2	1.9
Benton test										
Correct	5.2	1.5	⟷	2.2	1.6	⟷	4.0	1.5	3 2	1.7
Errors	8.0	2 9	⟷	13.0	3 3		9.6	4.0	10.5	3.1
Progressive Matrices	21.6	5.3		17.2	6.0		21.1	0.5	18.2	2.1
WCS										
Correct	82.6	18.0		65 8	14.8		67.0	7 5	66.2	14.5
Criteria	4.8	1.2		3.2	1.8		3.7	1.3	3.0	1.1
SCF										
Correct	57.2	9.3	⟷	45.3	4.5		46.8	10.4	48.7	12 2

* Percentage of hemisphere volume. Arrows indicate U-test probabilities below 5 per cent. For abbreviations, *see* footnote to Table 2.

TABLE 4 COMPARISON OF NEUROPSYCHOLOGICAL TEST RESULTS FOR PATIENTS WITH SMALL UNILATERAL THALAMIC LESIONS, SITUATED ROSTRALLY AND CAUDALLY ACCORDING TO CT SCAN

	Rostral lesions			*Caudal lesions*	
	$\bar{X}$	*SD*		$\bar{X}$	*SD*
	n = 5			n = 5	
Lesion size*	0.26	0.16		0.24	0.30
Age	55.6	10.2		59.8	3.1
Full scale IQ	92.2	11.5		92.2	12.1
Verbal IQ	94.6	6.5		95.2	9.4
Performance IQ	90.2	15.0		89.8	13.2
Digit Span	8.2	1.6		9.2	2.7
Arithmetic	6.8	2.0		7.4	2.1
Similarities	8.8	0.8	⟷	6.4	2.1
Picture Arrangement	7.0	3.2		7.0	2.3
Block Design	6.8	2.3		6.0	2.5
Benton test					
Correct	3.8	1.9		2.8	1.8
Errors	9.4	5.6		12.2	3.0
Progressive Matrices	19.4	5.2		20.4	7.1
WCS					
Correct	73.6	13.1		59.8	14.1
Criteria	4.0	1.9		2.8	0.8
SCF	41.6	5.3	⟷	53.5	10.2

* Percentage of hemisphere volume. Arrows indicate U-test probabilities of less than 5 per cent. For abbreviations, *see* footnote to Table 2.

For a comparison of the cognitive disturbances resulting from rostral as opposed to caudal thalamic lesions we subdivided them at the massa intermedia (or at the waist of the third ventricle) (Table 4). Three patients, whose lesions were situated on both sides of the dividing line, were excluded. Size of lesion, age and IQ were comparable between patients with rostral and caudal lesions.

Patients with rostral lesions showed markedly lower scores for Sequential Concept Formation and performed slightly worse for Digit Span, whereas patients with caudal lesions were impaired in the Similarities, Wisconsin Card Sorting and, to a lesser extent, the Benton test. Performance in the rostral group was close to that for the group with white matter lesions in the Similarities, Wisconsin Card Sorting and the Benton test, and for the posterior group in Digit Span and Sequential Concept Formation. Although these findings, except for Similarities and Sequential Concept Formation tests, are far from significant, they might indicate specific cognitive deficits resulting from thalamic lesions due to different functions of rostral and caudal thalamic nuclei.

DISCUSSION

The results of this study indicate first that small unilateral thalamic lesions lead to a general although not severe impairment of cognitive function. Similar but less pronounced deficits were found with white matter lesions of significantly larger size. Secondly, there is no evidence for specific deficits associated with left or right thalamic lesions. On the whole, patients with left-sided lesions performed worse, seen particularly for a visuoconstructive short-term memory test. Thirdly, there is some evidence for a dissociation between rostral and caudal thalamic disturbances, with rostral lesions leading to a deficit of learning and retrieval of series and posterior lesions to one of 'abstraction' and categorization.

The first two findings would support theories of a nonspecific thalamic participation in cognition, as has been suggested by Riklan and Levita (1969, 1970), whereas the third indicates more specific deficits resulting from the thalamic lesions. Theories which postulate an entirely cortical representation of higher mental function would have predicted that cognitive deficits would be more severe with white matter lesions than with lesions of the deep nuclei of the brain, because only the first could give rise to corticocortical disconnection. This was not confirmed by the findings of the present study.

A solely cortical representation of cognitive functions would, however, be compatible with generalized cognitive deficits due to thalamic lesions, if the role of the thalamus was restricted to nonspecific behavioural functions, such as alerting, vigilance, concentration and directed attention (Riklan and Levita, 1969, 1970; Brown, 1974; Luria, 1977). This view is supported by the results obtained when we compared for laterality. We found no evidence for a lateralization of verbal functions to the left and visuoconstructive and perceptive functions to the right at the level of the thalamus. This is contrary to other reports (for example, Reynolds *et al.*, 1979; Cappa and Vignolo, 1980; Vilkki, 1978). The difference might be related to the time at which testing was performed. We investigated our patients months to years after their episode, whereas reports concerning lateralized deficits, with few exeptions (van Buren, 1975), rely on findings obtained during the acute stages. This points to a marked compensatory capacity for deficits resulting from unilateral thalamic lesions, probably by the opposite thalamus. We doubt whether our inability to demonstrate effects of lateralization is a result of inadequacies of technique, as marked laterality effects of language-dependent deficits to left and visuoperceptive to right lesions can be demonstrated with basal ganglia lesions (Wallesch *et al.*, 1982).

In agreement with studies of patients with bilateral lesions (von Cramon and Eilert, 1979; Schott *et al.*, 1980), we found a deficit in patients with unilateral rostral thalamic lesions in a test of learning and retaining a sequence, which was paralleled by comparatively small digit spans. The short-term retention of visual patterns, however, was relatively undisturbed. A participation of rostral thalamic nuclei in memory mechanisms has been suggested by Victor *et al.* (1971) who, like Riggs and Boles (1944), reported that besides involvement of the mamillary bodies and other structures, there were lesions in the dorsomedial nuclei in patients with Korsakov's syndrome. These nuclei, and their connections to the hippocampus and the limbic cortex, are important in a theory of memory storage based on an information theory approach (Kornhuber, 1973).

On the other hand, patients with unilateral caudal lesions of the thalamus showed impairment in the Wechsler Scale subtest Similarities and the Wisconsin Card Sorting test, whereas they performed almost normally for Sequential Concept Formation and Digit Span. The Similarities as well as the Wisconsin Card Sorting tests require the ability to categorize and analyse. Although an impairment for both tests is described for patients with frontal lobe lesions, and the Wisconsin Card Sorting test is widely considered to be specific for deficits related to frontal lobe pathology (Lezak, 1976), we consider it more likely that various functions are required in order to succeed in this task, some of them being represented in the frontal lobe, some in other parts of the brain. The strong connections of the pulvinar with the retrorolandic cortex might be the anatomical substrate of the thalamic involvement in these functions.

The dichotomy of cognitive deficits found with rostral as against caudal thalamic lesions is in favour of additional specific cognitive functions by this nucleus, whereas the overall cognitive deficits of both groups again support theories of somewhat nonspecific behavioural effects of thalamic lesions in tests of cognitive function.

The tests used in this study, however, can only serve as a screening procedure for neuropsychological deficits, the results of which hopefully may lead to, but cannot answer, specific questions as to the participation of the thalamus in higher mental function.

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OSCILLOPSIA AND RETINAL SLIP

EVIDENCE SUPPORTING A CLINICAL TEST

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SUMMARY

A clinical bedside test for oscillopsia is described for patients suffering from an acute deficiency of compensatory eye movements due either to inappropriate pursuit eye movements or a defective vestibulo-ocular reflex (VOR). This test involves quantitative measurement of the amplitude of apparent image motion (oscillopsia) during head oscillations with frequencies of 1 or 2 Hz, ±20 deg amplitude. It was found that normals show no oscillopsia at 1 Hz whereas patients with acute disorders do. In subacute diseases of eye-head co-ordination, however, recordings of head and eye movements revealed a dissociation between net retinal slip and oscillopsia, with the magnitude of the latter being appreciably smaller than the former. This was interpreted as indicating a central suppression mechanism initiated by the acute eye movement deficiency. The results are discussed in terms of an inhibitory interaction between self and object motion perception which produces elevated thresholds for the detection of image motion.

INTRODUCTION

It has been observed clinically that patients with external eye muscle paresis are often unable to recognize faces or read while walking and report motion of stationary visual scenes during head motion or locomotion, a phenomenon termed *oscillopsia* (Brickner, 1936). In addition, it is also known that in diseases causing involuntary ocular oscillations (for example, acquired pendular nystagmus, downbeat nystagmus, superior oblique myokymia) oscillopsia also occurs (Bender, 1965).

One possible cause for this distressing apparent motion due to retinal image motion in cases of infranuclear eye movement defects is an inappropriate gain of the vestibulo-ocular reflex (VOR). The VOR normally serves to hold the direction of gaze in space constant during head movements by driving the eyes to move in their orbits in the direction opposite to that of head motion with a velocity and amplitude which 'compensates' for the head motion. If the amplitude and/or velocity of eye movements are inappropriate, the result is a shift in the direction of gaze causing a displacement or slip of the retinal image which may be perceived as an apparent motion of the fixated object. As appealing and simple as this model is, it is not supported by recent studies. It has been shown that for healthy subjects *even under* *optimal fixation conditions*, either with a biteboard or with subjects sitting or standing as still as possible (Stavenski *et al.*, 1979), or with head oscillations (Steinman and Collewijn, 1980), appreciable displacements of retinal images result, with velocities ranging between 20 min of arc/s (biteboard) to an average of 4 deg/s (head oscillations). In spite of such retinal image velocities, oscillopsia is not reported. Thus a stable world may be perceived even if the 'compensatory' eye movements initiated by the VOR are not sufficient to cancel the retinal image motion.

Oscillopsia may also occur in disorders involving involuntary ocular movements which override fixation in the absence of concomitant head motion, and therefore without the involvement of the VOR. Here it is excessive rather than deficient eye movements which lead to the retinal motion of objectively stationary objects. Patients with such disorders also report oscillopsia.

Bender and his coworkers described clinical cases of patients in which oscillopsia was presumably due to a deficient VOR but also cases without any measurable oculomotor disturbances (Bender, 1965; Bender and Feldman, 1967; Atkin and Bender, 1968; Gresty *et al.* 1977). The only other functional tests of inappropriate eye movements have been reported by Benson and Barnes (1978), using visual acuity, as well as by Zee (1978) who observed relative movements of the optic disc by means of ophthalmoscopy during active head movements.

The purpose of our investigation was twofold:

1. To obtain quantitative data on head-eye co-ordination in order to determine to what extent oscillopsia is due to net retinal slip during head motion. Head-eye co-ordination was therefore measured during sinusoidal rotary head movements about the vertical z-axis (yaw) during fixation of a static target in the median plane. This procedure allowed a comparison of net retinal slip with oscillopsia. Our measurements took into account the fact that asymmetric vergence occurs during head movements, a factor which has been neglected in the previous literature.
2. To devise a simple clinical bedside test of oscillopsia as a symptom which might be useful in the diagnosis of ocular motor disorders or vestibulo-ocular reflex deficiencies. Since oscillopsia occurs physiologically beyond a critical frequency and velocity of head motion, such a test should permit a relatively easy and reliable differentiation between physiological and pathological oscillopsia. It should be stressed here that clinical experience has shown that oscillopsia is most pronounced in acute disturbances but subsides or may even disappear with progress of the condition. This fact will be evident in the clinical data presented.

METHODS

Oscillopsia during Head Oscillation (*Oscillopsia Test*)

One of the purposes of this study was to develop a simple clinical test for oscillopsia with the testing situation as uncomplicated as possible. A 10 cm square target constructed out of black cardboard and containing a white disc in its centre (1 cm diameter) was affixed to a screen in the median plane at eye level (fig. 1A). The subject stood 1 m from the screen, unless otherwise indicated, and was instructed to make rotatory head movements about the vertical z-axis as shown in fig. 1A with a frequency of either 1 or 2 Hz. A metronome was used to aid the subject in achieving and maintaining these frequencies. The experimenter monitored the amplitude of head movements by noting the alignment of the head with two marker discs affixed ±20 or ±30 deg laterally and below the line of sight to the subject. Usually subjects were able to make appropriate head movements after 10 to 15 practice oscillations. Subjects were instructed to maintain fixation on the small white disc during head movements and to note whether the fixated target appeared to move during such head movements. If motion was reported, head motion was stopped and the amplitude of this motion was determined quantitatively. The experimenter held a strip of paper against the screen, one end of which abutted on either the left or right edge of the fixation target. The experimenter then moved a vertically orientated pencil along the paper strip either towards or away from the target until the subject said stop. This position was marked with the pencil on the paper strip, and the procedure was repeated for the other side of the target. These marks represented the reported amplitude of target oscillation during head movements, and expressed in degrees of visual angle constituted a simple psychophysical measure of oscillopsia. Neither patients nor normal subjects found this task difficult.

Measurement of Eye-head Co-ordination and Retinal Slip: Description of a Method Correcting for Ocular Vergence

When head and eye movements were simultaneously recorded, the subject or patient was seated 120 cm before a curved screen and wore a tightly fitted earphone device which allowed only lateral rotation of the head about the vertical z-axis. Head movements were recorded by means of a potentiometer and appropriate amplifiers. Eye movements were measured by means of electronystagmography, separately for each eye.

The studies on oscillopsia previously cited (Bender, 1965; Bender and Feldman, 1967; Atkin and Bender, 1968; Gresty *et al.*, 1977) did not take into account the problem of asymmetric vergence during head movements. These authors simultaneously recorded rotary head movements around the z-axis and eye movements in several patients in order to assess the intactness of the VOR. In addition to assuming in their work that the compensation of head oscillation is complete in normals, their investigations suffered from a second deficiency. In order for the VOR to be judged intact, it is *not* true that the amplitude of eye movements must be identical to that of head movements but simply 180 deg out of phase. The reason for this is that the axis of rotation of the eye and the head differ because of the forward and lateral displacement of the eyes in the head. This means that the required angular compensation of the direction of gaze in the two eyes is increased due to the necessity of asymmetric vergence in maintaining fixation. Blakemore and Donaghy (1980) as well as Collewijn *et al.* (1981) have independently noted and discussed the two-axis problem in eye-head co-ordination in the cat and man, respectively.

Fig. 1B shows that in order for the VOR to be completely compensatory, that is, holding the direction of gaze in space constant in spite of head rotation, the eye must rotate with an angle *exceeding* that of the head. In this figure α represents the angle of head rotation. It can be seen that an angle of rotation equal to α but in the opposite direction does not suffice to hold fixation on the target (T). An additional angle of rotation, β, is required to accomplish this. The magnitude of β increases with the angle of head rotation, α, as depicted in fig. 1C. It can be seen here that for an angle of head rotation of 20 deg, β is equal to about 2 additional degrees. Also evident in fig. 1C is the fact that β is slightly influenced by the

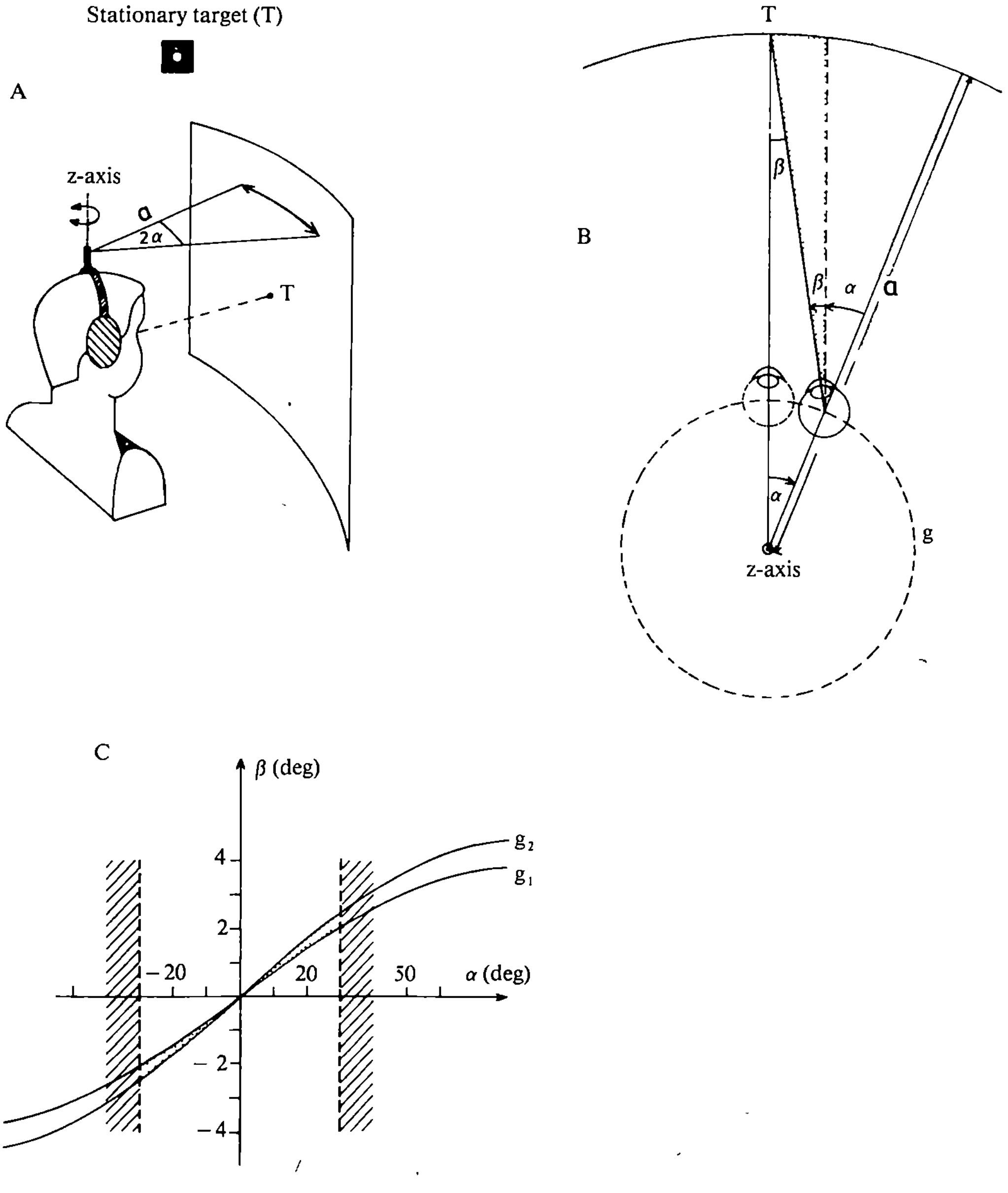
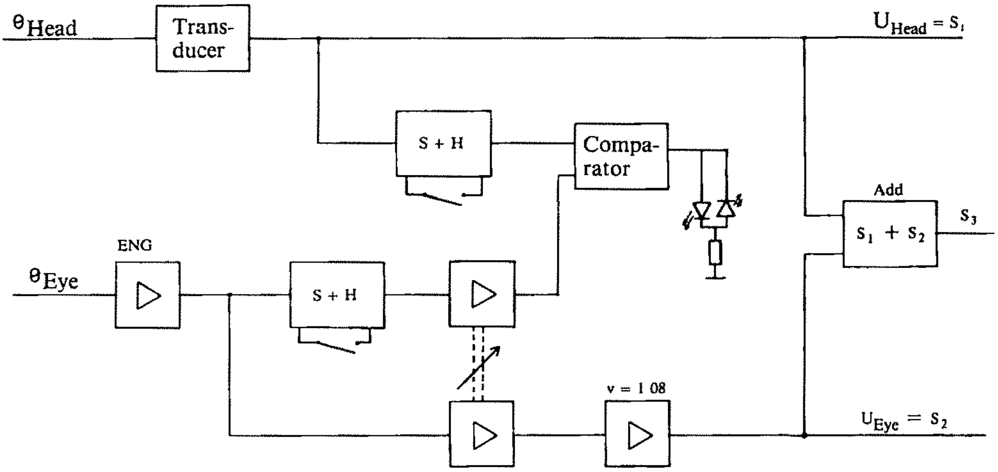


FIG 1. A, schematic representation of the experimental procedure for the measurement of eye-head co-ordination and retinal slip during oscillatory head movements about the vertical, z-axis with fixation of a stationary target. B, geometrical representation of the different angles of head and eye rotation required in order to maintain fixation on the target during head oscillation. For an accurate determination of eye-head co-ordination, it is necessary to calculate the required additional rotation of the eye (β) which results from the different axis of rotation of eye and head. C, β as a function of angular head displacement for a distance of 1.2 m between z-axis and fixation target. α = Angle of head rotation. $\alpha+\beta$ = Angle of eye rotation. β = Additional angle of eye rotation g = Head circumference (g_1 = 0.51 m, g_2 = 0.61 m). a = Target-z-axis distance (a = 1.2 m).

$$\beta = \arccos \frac{2\pi a - g\cos\alpha}{\sqrt{(2\pi a)^2 + g^2 - 4\pi a g \cos\alpha}}$$

circumference or girth (g) of the head; g_1 and g_2 ($51 \leq g \leq 61$) represent extremes of normal head girth. The equation shown at the right in fig. 1 expresses the relationship between head girth and displacement of the centre of rotation of the eye due to head movement about the z-axis. Direct measurement of CT scans allows the assumption that the centre of rotation of the eyes can be regarded as lying on the circumference of a circle, provided that the z-axis is located at the mid point of the line connecting the two mastoid processes (relative error ≤ 5 per cent). It should be noted that for geometrical reasons, β is also dependent upon the distance between the head and the fixated target (as fixation distance increases, β decreases). Thus if the direction of gaze is to be held constant during head motion, the mechanism underlying the VOR must be adjusted to the distance of the fixated target.



$$fs_3 = \frac{\Delta s_1 + \Delta s_2}{s_1 - s_2} \cdot 100\% \text{ (relative fault)}$$

FIG. 2. Block diagram for registration of eye-head co-ordination. Determination of retinal slip electronic circuit developed to avoid the inappropriate simple summation of head and eye movement signals. This circuit serves to calibrate the relationship between head and eye movement signals so that the final output (s_3) represents the actual displacement of the eye relative to the head. With this circuit a calibration for eye and head signals is avoided by means of amplifiers, two Sample and Hold (S+H) elements and a comparator. Furthermore, the differential rotations of eye and head required for stabilization of gaze is electronically taken into account (amplifier labelled $v = 1.08$). When the vestibular ocular reflex is intact, the combined signal (s_3) shows an oscillation representing the differential absolute displacement of eye and head.

Fig. 2 is a block diagram of the electronic circuit developed by S. Krafczyk in order to avoid the error of simply summating head and eye movement signals. This circuit serves to calibrate the head and eye movement signals, so that the final output (s_3) represents the actual displacement of the eye relative to the head. Here the relationship between α and β was linearized (which is permissible for angles of rotation of ≤ 30 deg) such that the gain (ratio between the angles of eye and head rotation: 21.6/20 deg $= v = 1.08$) was considered to be a constant. The additional required rotation of the eye, β, is electronically taken into account by the amplifier labelled $v = 1.08$. When the VOR is intact, the combined signal (s_3) shows an oscillation with an amplitude equal to β rather than a straight line

EXPERIMENTAL PROCEDURE AND RESULTS

Experiment 1. Yaw Head Oscillations and 'Hopping' in Normal Subjects

Eighteen male and female university students between 20 and 28 years of age were tested for oscillopsia under the conditions devised for the simple clinical bedside test. All subjects were tested with both binocular and monocular fixation of the target shown at the bottom of Table 1. For the rotary head movements about the vertical *z*-axis (yaw), we wished to determine whether a difference in psychophysically measured oscillopsia existed between active and 'passive' head movements. For the 'passive' condition, the experimenter positioned himself directly behind the subject who was instructed to relax his neck muscles. The head was held firmly in both hands and laterally rotated ±30 deg in time with a metronome set at 2 Hz.

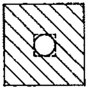
As a crude check on the adequacy of fixation during head movements, an after-image condition was included. An electronic flash unit, masked to yield a square aperture equal in dimensions to the diameter of the small white fixation disc, was centred directly over this disc and fixated by the subject. It was removed immediately after the flash and the subject was requested to note whether it moved during head movements. Subjects typically reported either that the apparent displacement of the after-image was *less* than that of the fixation target or that they were unable to detect any oscillation of the after-image. No subjects reported oscillopsia at 1 Hz.

Table 1 contains the data obtained for the 2 Hz condition. As can be seen in this table, mean displacement of the fixation target ranged between ±1.47 deg for hopping at 2 Hz with an after-image to ± 3.95 deg for passive yaw movements of the head without an after-image. Oscillopsia was significantly less for the monocular

TABLE 1. EXPERIMENT 1. YAW AND HOPPING MEAN APPARENT DISPLACEMENT OF FIXATION TARGET (OSCILLOPSIA, DEGREES) FOR LATERAL HEAD MOVEMENTS OF ±30 DEG AT A FREQUENCY OF 2 HZ AS WELL AS FOR HOPPING AT 2 HZ (18 NORMAL SUBJECTS)

	Lateral head movements					
	Active		*Passive*		*Hopping*	
	With AI	*W/o AI*	*With AI*	*W/o AI*	*With AI*	*W/o AI*
Binocular	±3.09	±3.57	±2.78	±3.95	±1 64	±1.70
	(2.79)	(3 50)	(2.31)	(3.87)	(0.88)	(0 85)
Monocular	±2.57	±2.74	±2.11	±2.14	±1 47	±1.55
	(2.17)	(2.22)	(1.88)	(1.90)	(0.76)	(0.98)

Measurements were obtained with both monocular and binocular fixation of the target shown at the bottom. Subjects typically reported either that the apparent displacement of the after-image was *less* than of the fixation target or that they were unable to detect any oscillation of the after-image. Mean apparent displacement of fixation target in degrees and SD (parentheses). n = 20: *AI = after-image. Fixation target = 10 cm (5 73 deg). Distance = 1 m. Fixation disc = 1 cm (0.573 deg). After-image = square, 1 cm (0 573 deg)



than for the binocular yaw movements of the head for both the active ($t = 1.7769$, $df = 19$, $P < 0.05$, two-tailed test) and the passive conditions ($t = 2.6779$, $df = 19$, $P < 0.01$, two-tailed test) when after-image was not present. Although significantly less oscillopsia occurred for the hopping conditions than for the yaw movements, this difference is attributable to differences in the amplitude of head displacement between these conditions and probably also to the plane of the compensatory eye movements (vertical for hopping and horizontal for yaw movements).

The difference between monocular and binocular vision during yaw movements is most probably due to the fact that double images result in the latter condition thus increasing the total apparent amplitude of target displacement. No significant difference between active and passive yaw movements of the head was found.

Experiment 2. Yaw, Hopping, Roll and Pitch Head Oscillations in Normal Subjects

In this experiment oscillopsia occurring in conjunction with two other types of head oscillation was investigated: pitch movements about the horizontal y-axis through the ears and roll movements about the line of sight. A total of 40 male and female university students with the same age distribution as in the first experiment were employed. The same procedure was used.

No differences between monocular and binocular conditions were found except for the hopping condition where oscillopsia was significantly greater for binocular fixation ($t = 3.1586$, $df = 39$, $P < 0.005$, two-tailed test). As in Experiment 1, no significant differences between active and passive yaw movements were found for either binocular ($t = 0.20.85$, $df = 39$, n.s. two-tailed test) or monocular viewing ($t = 1.0665$, $df = 39$, n.s. two-tailed test). Significantly greater oscillopsia amplitudes were found for active, binocular yaw movements than for pitch ($t = 4.2756$, $df = 39$, $P < 0.005$, two-tailed test) and roll movements ($t = 3.8249$, $df = 39$, $P < 0.0005$). These significant differences are probably due to differences in the form, velocity, and amplitude of the different head motions as well as to differences in the degree

TABLE 2. EXPERIMENT 2 ROLL AND PITCH

	Head movements				
	Lateral				
	Active	*Passive*	*Pitch*	*Roll*	*Hopping*
Binocular	±2.10	±2.67	±1.31	±1.10	±1.97
	(2.01)	(2.15)	(1.31)	(0.72)	(0.61)
Monocular	±1.68	±1.77	±1.12	±1.00	±1.57
	(1.21)	(1.22)	(0.69)	(0.71)	(0.83)

Mean apparent displacement of fixation target in degrees and standard deviations (parentheses). $n = 40$. Fixation target same as in experiment 1. Mean apparent displacement of the fixation target (oscillopsia, degrees) as in Table 1 but for different groups of normal subjects. Oscillopsia was determined for passive as well as for active head movements of ±30 deg at 2 Hz as well as for hopping at 2 Hz. Fixation was either monocular or binocular. The individual values for the head tilting movements were typically the smallest, probably because the subjects were unable to maintain the 2 Hz frequency.

to which retinal image motion was compensated for by eye movements. Oscillopsia was typically not reported for the 1 Hz condition, with the exception of occasional reports for the hopping condition.

It should be noted here that in both experiments each subject was tested only once for each condition because after repeated testing in pilot studies, subjects complained of dizziness, headache, and mild nausea, which may be regarded as early symptoms of motion sickness. This observation of motion sickness after active head movement is especially interesting since motion sickness is typically regarded as being induced by passive head motion resulting from transportation in vehicles. Motion sickness after active head movement has previously been reported only when a mismatch between visual and vestibular inputs exists, as, for example, when inverting prisms are worn (Melvill Jones and Mandl, 1981). Furthermore, we have informally observed, after repeated testing of ourselves and selected subjects, that the magnitude of oscillopsia appears to decrease upon repeated testing. This is suggestive of an exposure-dependent suppression mechanism.

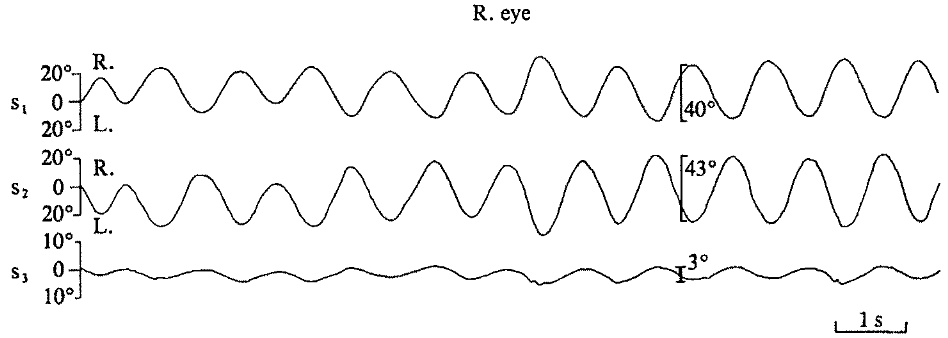


FIG 3. Original recording obtained from a normal subject (male, aged 39 yrs). In the top line head oscillations of approximately ±20 deg at a frequency of roughly 1 Hz are represented. The second line shows the out of phase eye movements, while the 3 deg calibration in the third line represents the amount of eye displacement in excess of head displacement required to maintain the direction of gaze in space (β). The average amount of additional eye displacement for this typical normal subject was 3 deg. No oscillopsia was reported s_1 = head oscillation. s_2 = eye oscillation. $s_3 = s_1 + s_2$.

Experiment 3. Oscillopsia and Retinal Slip in Infranuclear Oculomotor Disorders

Measurements of the net retinal slip of the fixation target employing the circuit described in fig. 2 were compared with oscillopsia using the psychophysical method of the preceding two experiments. Fig. 3 is an example of a recording from a normal subject. The upper tracing (s_1) represents yaw (rotatory head movements) with a frequency of 1 Hz and an amplitude of ±20 deg. The second tracing (s_2) represents eye movements, while the third (s_3) gives the amount of eye displacement in excess of head displacement (3 deg), required in order for the direction of gaze in space to remain constant during head movements. This subject's VOR was intact, since an excess eye displacement of ±1.5 deg was obtained which is equal to β.

It should be emphasized here that none of the 58 subjects in Experiments 1 and 2 when tested for oscillopsia during yaw head movements at 1 Hz reported oscillopsia.

In the following, clinical examples of monocular infranuclear oculomotor disorders will be presented in which subjective oscillopsia was largely suppressed in spite of considerable retinal slip. Fig. 4 is a recording obtained from a 69-year-old male patient with a subacute abducens palsy of the left eye. As can be seen in the dashed portion of the record for the left eye in the second line (s_2), movements to the left were deficient in amplitude; β for this patient was equal to 4 deg while an average amplitude of 8 deg is evident in s_3. Thus the amount of retinal slip was $8-4 = 4$ deg.

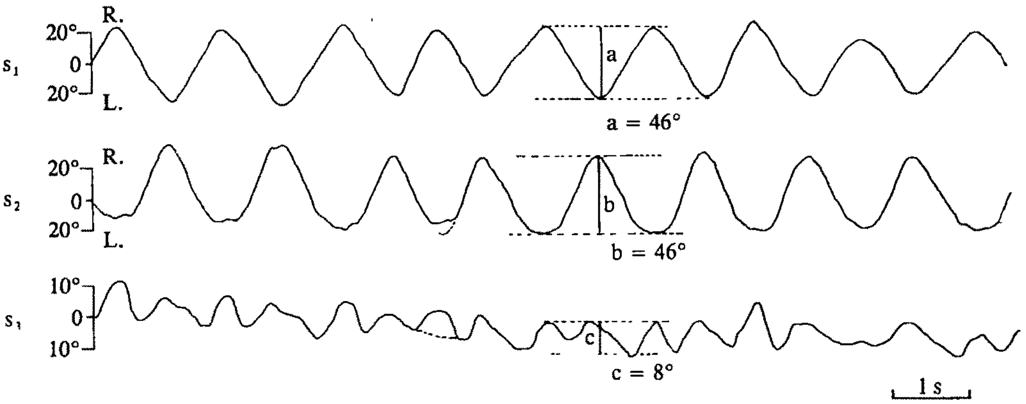


FIG 4 Original recording obtained from a patient with a subacute abducens palsy of the left eye. As shown in the second line the displacement of the eye to the left was too small The amplitude of head displacement was ±23 deg at a frequency of 0 8 Hz. For this head movement, β was 4 deg, while the mean excess eye displacement was in fact 8 deg. Thus this patient showed a retinal slip of 4 deg but reported no oscillopsia Subjective oscillopsia = 0 deg. Retinal slip = 4 deg = (8–4 deg).

The calculated maximal retinal velocity was 10 deg/sec. This patient reported no oscillopsia in spite of considerable retinal slip. The frequency of head movements in this record was 0.8 Hz.

Fig. 5 is a recording obtained from a 46-year-old male patient with a painful ophthalmoplegia, a Tolosa-Hunt syndrome, involving the superior orbital fissure or the anterior cavernous sinus of the left eye. In this patient some of the fibres of the third nerve were defective, resulting in weakness of the medial rectus muscle of the left eye. The upper half of the figure shows the results obtained from the healthy eye. β was equal to 4 deg and as shown below tracing s_3, the amount of retinal slip was 0, meaning that the VOR for this eye was intact. No oscillopsia was reported. The left eye tracing (lower half of figure), however, shows abnormalities. As can be seen in the eye movement tracing (s_2), amplitude was defective to the right. Since β was equal to 4 deg for this patient, and tracing s_3 shows an amplitude of 14 deg (frequency 0.66 Hz), a retinal slip of 10 deg was present. The maximal retinal velocity was 20 deg/s. In spite of this large retinal slip, the patient failed to report any oscillopsia. This recording was made about two weeks after the onset of his symptoms.

The last example, shown in fig. 6, is that of a patient with chronic ocular myasthenia gravis. Because of weakness of all the eye muscles, the total amplitude of eye movements during head movements was only 18 deg as compared to 40 deg for head movements at a frequency of 1 Hz. β was equal to 3 deg which, as shown below the third tracing, resulted in a retinal slip of 22 deg (maximum retinal velocity, 66 deg/s). Subjective oscillopsia amounted to 10 deg and was a distressing experience for the patient.

DISCUSSION

Clinical Test for Oscillopsia

The results of this study show that the choice of a proper combination of frequency and amplitude of head movements is critical for a sensitive test of oscillopsia. Rotatory head movement with a frequency of 1 Hz and an amplitude of ±20 deg proved to be a good base line condition for three reasons. (1) Stabilization of the retinal image in normals was complete within the measurement resolution of the electro-oculographic method (fig. 2). (2) No oscillopsia was reported at this frequency by normals. (3) This frequency amplitude combination represents a threshold condition, since oscillopsia is present in all normals at 2 Hz ± 20 deg. In this latter condition the maximum velocity of image displacement is 270 deg/s, which is too great to be compensated for either by pursuit or vestibularly induced eye movements. Since patients who may not report oscillopsia at 1 Hz should report it at 2 Hz, this condition can be employed with patients as a check on whether they are able to report oscillopsia at all. If the patient is unable to execute 2 Hz ± 20 deg amplitude head movements, the test may still be employed but with head oscillations of 1 Hz with the same amplitude and with the fixation distance reduced from 1 m to 20 cm. This, however, makes fixation difficult. Under these conditions, the necessary compensatory eye velocity is almost the same as that required for the normal test. The reason for this is that the amplitude and velocity of compensatory eye movements is dependent not only on the amplitude and frequency of head oscillation, but also on fixation distance.

The procedure for the performance of the test is very simple and requires little time. Essential for the test are the following conditions. (1) Location of a fixation disc, 1 cm in diameter attached to a wall at eye level. (2) Placement of the patient 1 m from the wall. (3) Instruction to the patient to fixate monocularly (one eye covered) on the disc while oscillating the head laterally to the beat of a metronome set at either

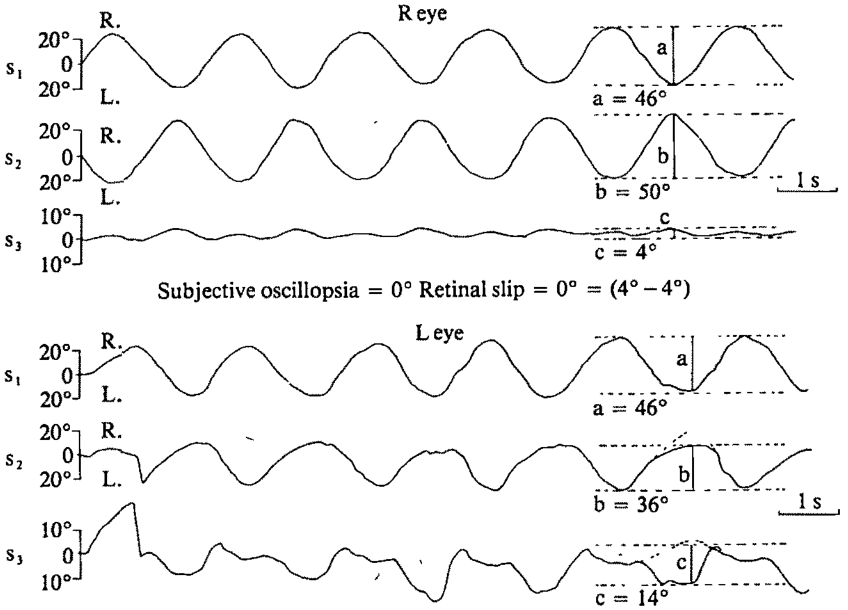


FIG. 5 Original recording obtained from a patient with a partial third nerve palsy (Tolosa-Hunt syndrome) in the left eye. Records for the normal right eye are shown above. In the third line, β was equal to 4 deg and retinal slip was 0. No oscillopsia was reported. For the left eye a retinal slip of 10 deg was demonstrated with a maximal retinal velocity of 20 deg/s. In spite of this, no oscillopsia was reported. Subjective oscillopsia = 0 deg. Retinal slip = 10 deg (14–4 deg).

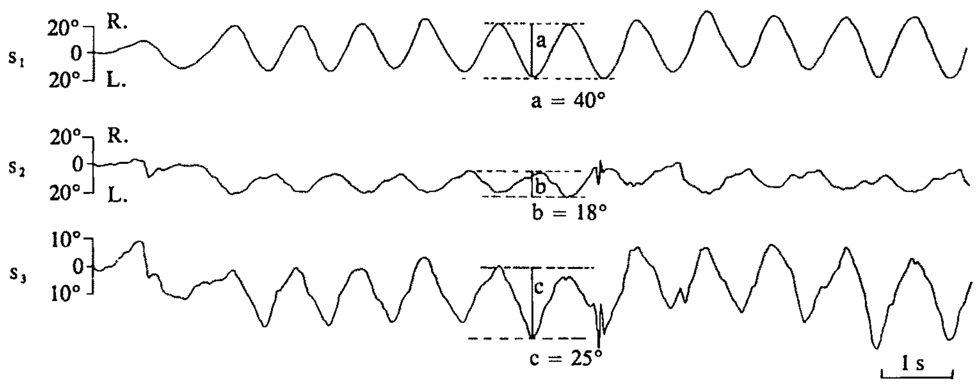


FIG. 6. Original recording obtained from a patient (aged 53 yrs) with a chronic ocular myasthenia of varying severity. Because of weakness of all eye muscles, the amplitude of lateral eye deviation was only ±9 deg (second tracing) The result of this was a calculated retinal slip of ±11 deg corresponding to a maximal retinal velocity of 66 deg/s. This patient reported oscillopsia which was indicated subjectively as ±10 deg in amplitude. Subjective oscillopsia = 10 deg. Retinal slip = 22 deg (25–3 deg).

1 or 2 Hz. (4) Measurement of the amplitude of apparent lateral motion of the fixation disc with a slip of paper and pencil.

If oscillopsia is reported at 1 Hz, pathology is indicated, since normals do not report oscillopsia at this frequency. Both patients and normals should report oscillopsia at 2 Hz. A negative test in cases of infranuclear disorders, as our data show, does *not* mean that the VOR is intact, but rather that suppression has taken place to such an extent that it is difficult to differentiate between patients and normals with this simple bedside test. This test is therefore particularly valuable for provoking this symptom in the early stages of these diseases, as well as in indicating the time course of the suppression of oscillopsia.

The suppression of oscillopsia may be apparently complete as shown in our extreme cases, with retinal slips of up to 10 deg without subjective illusory motion of the visual scene (figs. 4 and 5), but usually is only partial. The ratio of oscillopsia to net retinal slip has been measured in patients with chronic acquired ocular oscillations which override fixation (downbeat nystagmus) by Büchele *et al.* (1982) and was found to average 0.37 (fig. 7). Furthermore, patients with congenital nystagmus, who do not complain of oscillopsia in their usual direction of gaze, do so if nystagmus increases upon lateral gaze.

Suppression of Oscillopsia

The mechanism by which oscillopsia is suppressed, as in our patients with infranuclear ocular disorders, is not clear, although some evidence points towards a central mechanism. It has been found in cases of eye muscle paresis that after oscillopsia has largely been suppressed, the stationary paralysed eye has a higher threshold for the egocentric detection of single objects moving within the visual field than the healthy eye (D. Degner and Th. Brandt, unpublished). Furthermore, an inhibitory physiological interaction between self and object motion perception has been demonstrated by Büchele *et al.* (1980). During head oscillations, thresholds for the detection of object motion are elevated by a factor of 2.9 at 1 Hz±20 deg amplitude and by a factor of 6.5 at 2 Hz±20 deg amplitude. These findings imply that retinal slip during head motion may go undetected (absence of oscillopsia) because of an elevated threshold for the detection of retinal image motion. Therefore even in normals, the VOR need not stabilize the retinal image completely in order to prevent oscillopsia. Image motion is tolerated to a certain extent by the system because of the elevated motion detection threshold during head movements. Of course, this hypothesis does not explain why suppression for oscillopsia is so much dependent upon the time course of the disease in cases of infranuclear ocular disorders. The inhibitory interaction between object and self motion can only account for an immediate, modest reduction of oscillopsia. The gradual reduction and eventual disappearance of oscillopsia which occurs over days or weeks probably involves an additional mechanism which recalibrates the relationship between expected and actual retinal slip. This mismatch between actual and expected retinal slip constitutes the stimulus for this recalibration. In a telological sense, the

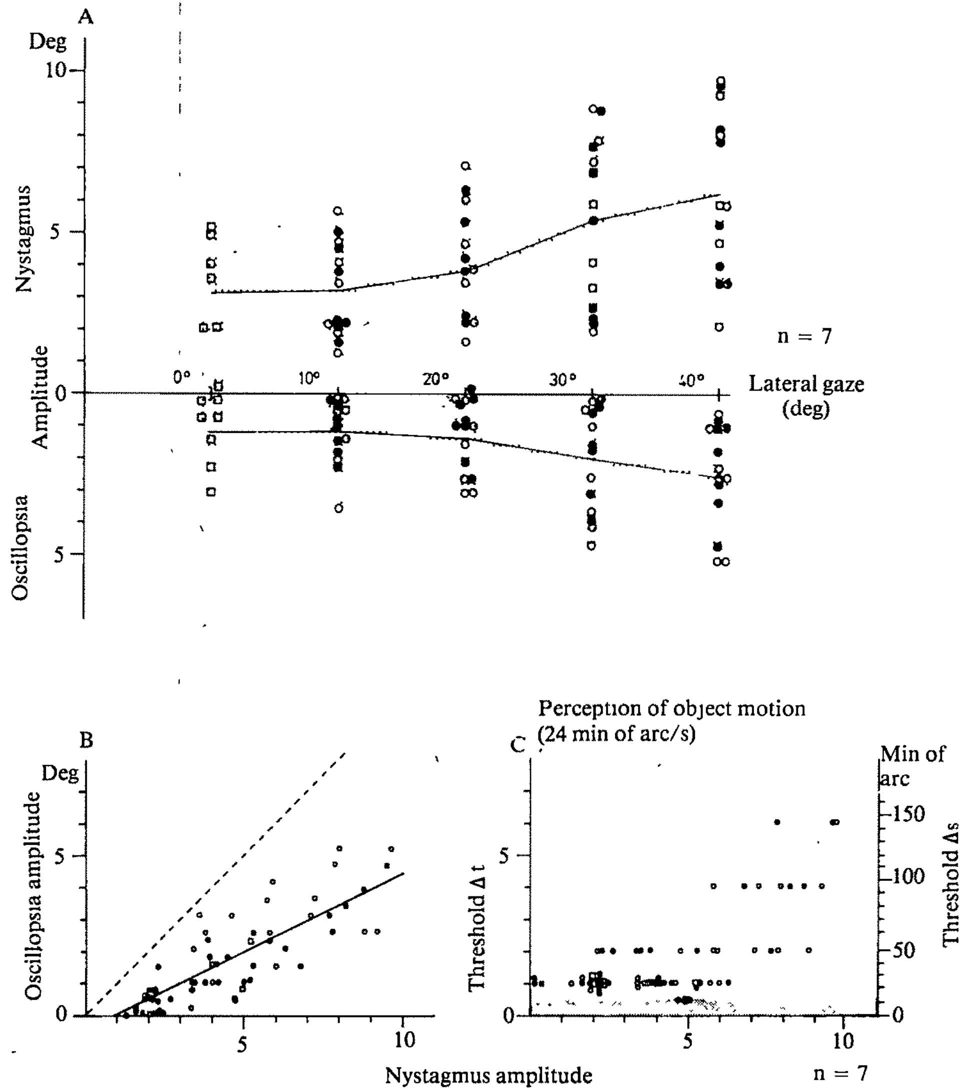


FIG. 7. A, mean nystagmus amplitude as a function of lateral gaze from 0 to 40 deg for 7 patients with downbeat nystagmus (upper half of fig.). The lower portion of this figure gives the mean reported oscillopsia of the same patients as a function of lateral gaze. It can be seen that both nystagmus amplitude and oscillopsia increase with increasing lateral gaze, although the former increases more sharply. The open circles indicate gaze to the right while the closed ones indicate gaze to the left. B, oscillopsia (ordinate) as a function of nystagmus amplitude (abscissa) for the same patients. Oscillopsia is always smaller than the net retinal slip (dashed line) but increases with increasing stimulus amplitude with a mean ratio of 0.37. C, thresholds for the perception of object motion as a function of nystagmus amplitude for the same patients. The shaded area represents the mean motion thresholds of normals. Motion detection thresholds increase with increasing nystagmus amplitude.

suppression of visual motion perception for both the retinal slip due to impaired eye movement as well as for single objects moving within the scene, is possibly related to a space constancy mechanism. This 'adaptive suppression' is beneficial to the organism to the extent that it alleviates the distressing oscillopsia with the disadvantageous side effect of impaired motion perception in general.

Why the Physiological Threshold of Oscillopsia Lies Between 1 and 2 Hz

The visual pursuit system alone is not capable of compensation for retinal slip during high frequency and large amplitude head movements. It has been found that pursuit movements of the eyes are adequate up to a frequency of 1 Hz. Maximum velocities of pursuit movements lie between 50 and 100 deg/s (Stark *et al.*, 1962). With large field stimulation, it has been found that slow phase optokinetic eye movements are adequate up to about 1.5 Hz (Trincker *et al.*, 1961). However, in the case of vestibular stimulation, compensatory eye movements may be adequate up to 8 Hz (Benson, 1970). Thus the vestibular system is responsible for higher frequency and velocity eye movements. Our proposed bedside test, therefore, is more sensitive for peripheral eye muscle disorders, whereas central changes in VOR gain preclude detection because of the low frequency head movements employed with this test. Visual stimulation alone can produce adequate eye movements up to a limit of only 1.5 Hz with an amplitude of ±10 deg. Therefore oscillopsia appears in cases with defective VORs of vestibular origin only with higher frequency head movements. The contribution of cervical receptors to the VOR is probably minimal and therefore insignificant. Barnes and Forbat (1979) found a cervico-ocular response with a gain of 0.05 during passive rotation of the body between 0.2 and 1.3 Hz with the head held stationary.

Under normal conditions during walking, for example, head motions varying between 1 and 4 Hz are produced (Gresty *et al.*, 1977). In normals, oscillopsia does not occur while walking since retinal slip is mostly compensated, while the residual slip velocity is probably below the threshold for motion detection. The pursuit system does not operate in this range and cannot be responsible for stabilization of the retinal image. Under the conditions of the present study, with large amplitude head motions of ±20 deg at a frequency of 1 Hz, the maximal velocity of image motion reaches 135 deg/s, a value in excess of the maximum velocity of pursuit eye movements (50 to 100 deg/s). In this case, it is necessary for the vestibular system to supplement the visual system in order to obtain compensatory eye movements of appropriate velocity. Our data show that image stabilization (within our error of measurement) results under this condition (fig. 2) and that for normals no oscillopsia is reported. Although the 2 Hz condition lies within the frequency range of the vestibular system, the large amplitude of ±20 deg requires eye movement velocities in excess of the capability of this system. This results in sizeable foveal retinal slip and the inevitable reports of oscillopsia by both normals and patients. A difference in VOR gain probably exists between active and passive head oscillation. For active oscillation, Tomlinson *et al.* (1980) found a maximal VOR gain of unity at about 1 Hz, which remains stable up to 5 or 6 Hz when it begins to decrease. For passive head oscillation, both Keller (1978, monkey) and Benson (1970, humans) describe a VOR gain greater than unity at high frequencies with a low frequency phase lead changing to a small phase lag above 3 Hz.

The CNS structure subserving eye-head co-ordination is the flocculus loop which is connected to the open loop VOR. The flocculus granular layer receives visual input concerning retinal slip *via* the accessory optic tract and has an inhibitory influence on the vestibular nucleus by means of the Purkinje cells. Microelectrode recordings have identified flocculus cells with a frequency modulation in relation to eye movements as well as gaze velocity, which indicates a summation of the signals of head and eye velocity (Lisberger and Fuchs, 1978).

Focal and Ambient Vision during Oscillopsia

Compensation of retinal slip by the VOR is not only important for relieving the distressing experience of oscillopsia, but is also of special importance for the control of postural balance. Since retinal slip is not confined to the fovea but involves the entire visual scene, it affects both modes of visual processing, focal and ambient, respectively. Consequently, retinal slip is used physiologically as an input for the visual regulation of postural balance. A mismatch between the expected and actual slip during eye and head movements will therefore have visuospinal consequences leading to an 'unexpected' body sway. The reports of dizziness, headache, and mild nausea obtained from our normals after repeated testing may be regarded as having been mediated by the ambient system.

In conclusion, we have devised and validated a simple bedside test for provoking and measuring oscillopsia quantitatively. Its advantage lies in its simple and rapid execution without dependence upon special equipment. Furthermore, when the results are positive with up to 1 Hz head oscillations, it provides a reliable measure of pathological ocular motility. It is especially suitable for acute peripheral ocular motor diseases and for the clinical control of their progress. Its disadvantages are that it is rather insensitive to central gain changes of the VOR, and is not suitable for the functional evaluation of chronic ocular motor disorders because of the marked suppression of this symptom in these cases.

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CHRONIC DEMYELINATING NEUROPATHY ASSOCIATED WITH BENIGN IgM PARAPROTEINAEMIA

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SUMMARY

Twelve cases of chronic sensorimotor neuropathy associated with benign IgM paraproteinaemia are described. The onset was in the sixth or seventh decades and 9 cases were male. Tremor and ataxia were common features. The ESR was raised in 6 cases and the CSF protein content elevated in 10. There was severe reduction of motor nerve conduction velocity. Sera from all cases contained monoclonal IgM antibodies strongly reactive with human peripheral myelin, made up by the paraprotein. Histological studies on nerve biopsies taken from 8 cases all demonstrated a demyelinating neuropathy. Eight biopsies were examined by immunofluorescence. Monoclonal IgM was present on the myelin sheaths of surviving myelinated nerve fibres. The findings suggested that the neuropathy was of autoimmune origin and caused directly by the antimyelin antibody.

INTRODUCTION

Peripheral neuropathy associated with myeloma is well recognized (Victor *et al.*, 1958; Hesselvik, 1969; Davis and Drachman, 1972; Sluga, 1974; McLeod and Walsh, 1975; Kelly *et al.*, 1981*a*). It may be the presenting feature, before there is any evidence of the underlying dyscrasia, and neuropathic symptoms can be subacute or insidious in onset, sometimes remitting spontaneously. The neuropathy may be motor, sensory or mixed sensorimotor in type. Motor conduction velocities are normal or reduced, sometimes markedly so. Morphological studies have shown the presence of axonal degeneration or segmental demyelination or a mixture of the two. Neuropathy is commoner in myeloma associated with osteosclerotic lesions, when it takes the form of a chronic demyelinating neuropathy resembling chronic progressive inflammatory neuropathy. Some of these cases have endocrine disturbances, hepatosplenomegaly and skin lesions, and this combination of abnormalities

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forms a distinctive syndrome (Iwashita *et al.*, 1977; Bardwick *et al.*, 1980; Kelly *et al.*, 1981*a*). In some cases of myeloma neuropathy, amyloid has been demonstrated in nerve biopsy specimens, in others direct infiltration of peripheral nerve trunks by myeloma cells has been observed, but in most cases these abnormalities were not found and the cause of the neuropathy was uncertain.

The paraprotein in myeloma and macroglobulinaemia can retain its capacity to act as an antibody (Waldenström *et al.*, 1964; Seligmann and Brouet, 1973). Morley and Schwieger (1967) have suggested that these antibodies may sometimes be specific for antigens in peripheral nerves and thus be the direct cause of the neuropathy. There is evidence to support this hypothesis, as Rousseau *et al.* (1978) have shown that IgA was bound to the surface of myelin sheaths in a nerve biopsy from a patient with IgA myeloma and neuropathy. Besinger *et al.* (1981) demonstrated that a neuropathy can be passively transferred to mice using serum from patients with myeloma neuropathy. Serum from myeloma patients without neuropathy was not effective.

Neuropathy is also found in Waldenström's macroglobulinaemia (McLeod and Walsh, 1975). It is clinically heterogeneous but spontaneous pain is often a feature. The cause of the neuropathy is unknown but again there is evidence for it being due to the paraprotein. Propp *et al.* (1975) and Julien *et al.* (1978) both reported single cases with reduced motor conduction velocities. Nerve biopsies revealed predominant segmental demyelination with IgM antibodies demonstrated by direct immunofluorescence, apparently localized to the surviving myelin sheaths. There were similar findings in the case of Nardelli *et al.* (1981) with an immunoperoxidase study. Carter and Lacey (1976) have found antibodies binding to neural tissues in the serum of patients with Waldenström's macroglobulinaemia and neurological symptoms.

Cases of neuropathy and benign IgG paraproteinaemia have been described. Read *et al.* (1978) reported 3 such cases, all of whom had neuropathies which remitted spontaneously. No antineural antibodies were detected in the serum. Dalakas and Engel (1981*b*) described 7 cases with a chronic sensorimotor neuropathy. Conduction velocities were normal or reduced. Two biopsies studied by direct immunofluorescence contained light chain fragments of immunoglobulin molecules on the outer parts of the myelin sheaths of surviving myelinated nerve fibres. Sewell *et al.* (1981) found serum antibodies binding to peripheral myelin in one case. IgG was present on myelin sheaths in a nerve biopsy specimen.

Chronic sensorimotor neuropathy associated with benign IgM paraproteinaemia has also been reported. The case of Thrush (1970) had a hypernephroma and the serum contained IgM antibodies directed against brain tissue. Forssman *et al.* (1973) described a patient whose nerve at biopsy was infiltrated by lymphocytes. Abundant IgM was demonstrated in these infiltrates using direct immunofluorescence. Case 10 of Chazot *et al.* (1976) had reticular deposits of IgM in a nerve biopsy specimen. The case of Fitting *et al.* (1979) had very slow conduction velocities. Deposits of a material resembling amyloid were found in the patient's nerve, but immunofluorescent studies were not performed. One case was reported by Swash *et al.* (1979) in which there was an associated carcinoma of the bronchus. The urine contained Bence Jones protein but there was no other evidence of immunocytic malignancy. Conduction velocities were reduced and a nerve biopsy specimen showed segmental demyelination with IgM localized to myelin. Dalakas and Engel (1981*b*) described 4 cases all with slow conduction. One had IgM localized to nerve fibres in a biopsy specimen, but no antineural antibodies were demonstrated in the serum. Finally, 4 cases reported by Latov *et al.* (1981*a*) had high titres of antiperipheral nerve myelin antibodies in their serum detected by complement fixation. These were of IgM class in the 3 cases tested. Latov *et al.* (1981*b*) have shown that the antigen is a protein in human peripheral nerve myelin with a molecular weight of approximately 100000 Daltons. Segmental demyelination was present in teased nerve fibres from one case (Latov *et al.*, 1980).

Thus there is evidence to suggest that the neuropathies associated with various paraproteinaemic conditions may be caused by the remote effects of a humoral factor secreted by neoplastic immunocytes, whether benign or malignant, and that this factor may in some cases be the paraprotein itself.

In this study we report 7 cases of neuropathy associated with benign IgM paraproteinaemia, derived from a survey of 56 patients with paraproteinaemia seen at a neurological centre over a three-and-a-half year period, together with 5 cases which have been studied since that time. Reports of some of the findings have been published (Bolton *et al.*, 1979; Kahn *et al.*, 1980, 1981).

PATIENTS

Selection and Clinical Assessment

During a period of three-and-a-half years, serum protein electrophoresis was performed as part of a routine liver function test profile on approximately 14000 sera from patients referred to the National Hospitals for Nervous Diseases. Fifty-six patients were found to have benign paraproteinaemia, 16 of whom had presented with peripheral neuropathy (Kahn *et al.*, 1980). The remaining 40 had a variety of neurological conditions and the class of their paraproteins was as follows: IgG (27), IgM (9), IgA (0), not tested (5) (one of the 40 had both IgG and IGM paraproteinaemia). In 4 of the 16 patients with neuropathy, well recognized causes of neuropathy were present (rheumatoid arthritis, IgM; diabetes mellitus, class not determined; lung carcinoma, IgG; and Guillain-Barré syndrome, IgM). Of the rest, 3 (one IgG, 2 IgA) showed substantially normal motor conduction velocities, and 9 severely reduced velocities (less than 50 per cent of the lower limit of normal in at least one peripheral nerve). Seven of these 9 cases had IgMκ paraproteinaemia, one an IgG paraprotein and a steroid responsive neuropathy, and the last a unique nonprogressive Bence Jones paraproteinaemia (S. N. Kahn, unpublished).

These 7 cases with IgMκ paraproteinaemia, peripheral neuropathy and slow motor conduction velocities, form the basis of the present report. All were examined by one of the authors (I.S.S.) and 5 by another author (P.K.T.). Details of the other 49 patients with paraproteinaemia were obtained from the case notes of the National Hospitals. Since the period of the survey, 5 further cases of IgM paraproteinaemia and otherwise unexplained neuropathy have been encountered. Three were examined by the above two authors and 2 by neurologists from other hospitals (Cases 8 and 9).

TABLE 1 SUMMARY OF CLINICAL AND PATHOLOGICAL OBSERVATIONS

Case No	*Age (yrs)/ sex*	*Length of history (yrs)*	*Tremor*	*Ataxia*	*ESR* mm/h^{-1}	*CSF protein* $g\ l^{-1}$ *(NR < 0.4)*	*Ulnar nerve* MCV $m\ s^{-1}$ *(NR > 49)*	*Paraprotein concentration* $g\ l^{-1}$	*Antimyelin antibody titre*
1	72/M	18	+++	+++	43	0.8	14	7	2560
2	71/M	16	+++	+++	55	1.2	12	12	5000
3	71/M	14	+++	+++	21	1.8	17	7	NQ
4	66/F	12	0	++++	62	1.3	7	7	5000
5	69/M	7	+	+	58	0.4	19	16	2560
6	69/M	7	+	0	5	0.7	34*	12	1280
7	62/M	7	+	+	26	1.0	18	8	5000
8	68/M	10	+++	++	46	NQ	22	NQ	NQ
9	60/F	10	+	+	12	1.8	6	11	5000
10	75/F	6	+	+	68	0.9	35**	3	5000
11	58/M	6	0	++	15	0.9	3.5	3	2560
12	56/M	3	+	+	3	1.0	23	5	1280

MCV = motor conduction velocity. NQ = not quantified NR = normal range * Peroneal nerve velocity = 17 $m\ s^{-1}$. ** Peroneal nerve velocity = 14 $m\ s^{-1}$ Tremor/ataxia 0 = none + = mild. ++ = moderate +++ = marked ++++ = severe.

Histories of the 7 original cases are given. The clinical features in the remainder were similar although their histories were usually shorter. In all, the family histories were negative and there was no relevant past medical history, nor significant exposure to alcohol, drugs, or other toxic agents.

Clinical Observations

Nine of the 12 patients were male (*see* Table 1). Apart from their neuropathies, all patients appeared well at their last follow-up (mean duration of neuropathic symptoms 9.8 years, range 3 to 18 years). The onset of the symptoms was insidious and always in the sixth or seventh decades They presented with paraesthesiae and then numbness in the feet, followed by similar troubles in the hands. Only Case 4 had spontaneous pain. This was felt episodically in the fingers and developed eight years after the initial symptoms. These sensory disturbances were followed by weakness and wasting of distal muscles, although in Case 6 only the feet were affected. The weakness was often overlooked by the patient when obvious to an examiner. One patient initially had sensory changes and weakness referrable to individual peripheral nerves, but later developed generalized abnormalities which suggested that this was not a multifocal neuropathy (Case 10). The symptoms were usually slowly progessive but often remained stable for some years, and there was occasionally spontaneous partial remission (Cases 1 and 12). Five patients had histories of Raynaud's phenomenon (Cases 2, 5, 6, 7 and 10) and the serum in one of these (Case 5) contained a cryoglobulin. The onset of this symptom was later than that of the neuropathic symptoms except for Cases 6 and 7 in whom it was in early adult life.

Examination of the cranial nerves was almost always normal. No sustained nystagmus was seen. The eye movements were full, and saccadic and pursuit movements were clinically normal except for Case 4 who could not follow a moving target smoothly.

In the limbs tone was normal or reduced and no fasciculation was seen. Tremor or ataxia were consistent findings. They sometimes appeared when the other motor and sensory signs were static and progressed slowly over the years while the weakness and sensory loss remained unchanged. Cases 1, 2, 3, 4 and 8 were those with the longest histories and they were also the cases who were markedly disabled by these movement disorders. Cases 4 and 11 had no tremor but were ataxic. All other 10 cases had tremor, although in 6 it was mild (Cases 5, 6, 7, 9, 10 and 12). In Cases 3, 7 and 10 it was present at rest. Case 3 had a typical 'pill-rolling' tremor but Cases 7 and 10 had tremor in the thumb without tremor in the other digits. In all these 10 cases, the tremor was evident in the fingers and hands when the arms were outstretched. It was increased by action, often markedly so, particularly during the terminal part of the movement. Ataxia in the legs was common although no tremor was ever observed.

The tendon jerks were usually absent except in the early stages of the disease. Sensation was impaired distally, although pain and temperature were often relatively spared. There were few complaints attributable to autonomic dysfunction. Only one patient had spontaneous pain (Case 4). These findings may reflect the sparing of unmyelinated fibres seen histologically. Joint position sense was grossly impaired in those cases with the most severe movement disorders apart from Cases 1 and 2 in whom it was only slightly reduced in the fingers.

General examination revealed no significant signs, there being no lymphadenopathy or hepato-splenomegaly. Case 6 had familial ichthyosis; his serum phytanic acid content was normal.

Case Reports

Case 1 (*NHQS No. A 34674*). The patient, a man aged 72 years, was a retired laboratory technician. At the age of 50 years he began to have episodes of pain in the back radiating into the right leg. Four years later, he developed persistent tingling sensations and numbness in both feet, followed by weakness at the ankles. A lumbar laminectomy was performed but no abnormalities were found. Postoperatively his symptoms were much worse and paraesthesiae were felt in his hands, which also became weak. Over the next two years he gradually improved and his condition was then stable for some years, although the symptoms did not fully resolve. At the age of 67 years, tremor appeared in his hands. It became so severe that he could not feed himself nor write legibly. His gait became unsteady, but he could still walk with a stick. All these symptoms were persistent apart from the paraesthesiae which have improved in recent years.

On examination, the cranial nerves were normal. Tone was normal in the limbs. There was marked wasting and weakness in the muscles of the hands and feet and lower legs. No tremor was present at rest, but there was a severe postural tremor in the arms, made worse by movement. The tendon reflexes were absent and the plantar responses were flexor. Superficial sensation was reduced distally. Joint position sense was slightly impaired in the hands and absent in the feet. His gait was moderately ataxic and he had bilateral foot-drop. The peripheral nerves were thickened. General examination was normal.

Case 2 (*NHQS No. A 96787*). The patient, a man aged 71 years, was a retired electricity inspector. At the age of 56 years he began to have episodes of discomfort in both feet, which he likened to walking on gravel. Five years later he noticed tremor in his right hand, only present during movement. A similar tremor appeared on the left after another three years. He then noticed weakness at the ankles which was slowly progressive. At the age of 64 years weakness in the hands was evident together with episodes of paraesthesiae. His gait became unsteady. All these problems were persistent and became steadily worse. When last seen he could walk with some assistance, but was severely disabled by the tremor in his arms.

On examination, the cranial nerves were normal. Weakness and wasting were marked in the hands and the lower legs. There was postural tremor in the hands, absent at rest and increased by action. Ataxia was present in the legs but there was no tremor. The tendon reflexes were absent and the plantar responses flexor. Superficial sensation and joint position sense were mildly impaired distally. His gait was ataxic with foot-drop. The peripheral nerves were normal to palpation. General examination revealed slight ankle oedema and absent foot pulses. The blood pressure was 180/100. No other abnormalities were found.

Case 3 (*NHQS No. A 81146*). The patient, a man aged 71 years, was a retired carpenter. When aged 58 years, he noticed unpleasant paraesthesiae in his feet which became slowly worse and were associated with numbness. Similar symptoms appeared in the hands six years later. His gait became unsteady with weakness at the ankles. Later his hands became weak and they were tremulous when he tried to use them. By this time the paraesthesiae were no longer unpleasant, but the numbness had persisted. When last seen, the tremor was the most severe problem. It was present at rest as well as during movement. He could still walk but was unsteady.

On examination, the cranial nerves were normal and in particular there was no evidence of parkinsonism. Tone in the limbs was normal. There was severe weakness and wasting in the lower legs, but only mild involvement of the hands. The hands were tremulous at rest. The appearance was that of the 'pill rolling' tremor characteristic of Parkinson's disease. It was increased during an actively maintained posture and there was a marked terminal tremor on movement. The legs were moderately ataxic. The tendon jerks were absent and the plantar responses flexor. Sensation for pain and light touch was impaired in the hands and below the knees. Joint position sense was very poor in the fingers and absent in the toes and ankles. His gait was wide-based and ataxic with foot drop. He had moderate nerve thickening. General examination revealed no significant signs.

Case 4 (*NHQS No. A 78387*). The patient, a woman aged 66 years, was a retired secretary. At the age of 54 years she developed tingling and then numbness in her feet and hands. These symptoms progressed and the paraesthesiae often had an unpleasant quality, made worse by heat. The paraesthesiae gradually disappeared over some years but the numbness persisted and spread as far as the knees and wrists. She first noted unsteadiness of gait at the age of 57 years. This was followed by difficulty in controlling her hands which interfered with her typing. By the age of 60 years she was severely disabled because of incoordination. Later she began to have bouts of spontaneous pain in the fingers. When last seen she was just able to walk using a frame, but was unable to dress or feed herself.

On examination, the cranial nerves were normal except that the ocular pursuit movements were irregular. However, these movements were full and there was no nystagmus. Tone in the limbs was reduced. There was mild wasting and weakness in the hands and feet. In the outstretched arms, the fingers moved in a choreiform manner but there was no tremor. She was grossly ataxic in all four limbs because of dysmetria, there being no intention tremor. The tendon reflexes were absent and the plantar responses were flexor. There was distal impairment of sensation for touch, with hyperpathia to pin prick. Joint position sense was absent in the fingers and toes and reduced at the wrists and ankles. Her gait was very ataxic. The peripheral nerves were not thickened. General examination was normal.

Case 5 (*NHQS No. A 79454*). The patient, a man aged 69 years, was a retired labourer. At the age of 62 years he began to have constant burning sensations in his fingers. Cold made this worse and also brought on attacks of pallor in the fingers, which would go red and tingle painfully on recovery. A few months later, the fingers became numb. His feet felt dead and would tingle if he sat down for too long. He often had an unpleasant burning sensation over the lateral aspect of the right thigh on lying or sitting. His gait became clumsy, his toes tended to catch the ground and his knees or ankles sometimes gave way. Two years later, he began to have difficulty with fine movements of the hands. Over the next five years these symptoms were persistent but did not worsen. However, during that time he developed a mild tremor in the hands which was present only on action.

On examination, the cranial nerves were normal. There was minimal wasting and weakness of the hands and feet. A slight tremor was present in the fingers when the arms were outstretched. He had an intention tremor on finger-nose testing, although this was not prominent. There was a little ataxia in the legs. The tendon jerks were absent and the plantar responses were flexor. Superficial sensation was reduced distally in the legs and also in the territory of the lateral cutaneous nerve of the thigh. It was normal in the hands apart from increased sensitivity to pin prick. Joint position sense was normal in the hands and impaired in the toes. His gait was slightly ataxic. The peripheral nerves were moderately thickened. General examination was normal.

Case 6 (*NHMV No. 81591*). The patient, a man aged 69 years, was a retired railway planning officer. At the age of 62 years he slowly acquired numbness in the feet, followed by tingling in the finger tips which spread, over the next few months, to involve the whole of his hands. When last seen these symptoms were still present and had progressed very little in recent years.

On examination, the cranial nerves were normal. There was no muscle wasting and power was normal apart from mild weakness in the toes. He had a fine postural tremor in the fingers. There was no ataxia. The ankle jerks were absent but the other tendon jerks were normal. The plantar responses were flexor. Pain sensation and joint position sense were normal. Sensation for light touch was impaired in the fingers and toes. Vibration sense was reduced in the feet. His gait was normal. There was no peripheral nerve thickening. General examination was normal apart from ichthyosis in the legs.

Case 7 (*NHQS No. A 82794*). The patient, a man aged 62 years, was an executive in an oil company. At the age of 54 years his feet gradually became numb and there was some tingling in his finger tips. His legs tired easily and his balance was uncertain. He found that writing was difficult, began to drop things and could not do up buttons. These symptoms slowly worsened over the next three years and he acquired numbness in the fingers and a tremor in the hands. Since that time all these complaints have been static.

On examination, the cranial nerves were normal. There was severe wasting and weakness in the hands, lower legs and feet. He had a little postural tremor in the hands, which was sometimes present in the thumbs at rest, with a mild intention tremor. The tendon reflexes were absent and the plantar reflexes unresponsive. Sensation for pain and light touch were impaired up to the wrists and knees. Joint position sense was normal in the hands and absent in the toes. His gait was slightly ataxic. The peripheral nerves were not thickened. General examination was normal.

INVESTIGATIONS

Routine Laboratory Investigations

All of the 7 original cases had the following investigations: full blood count, serum B_{12} and folate, blood sugar, blood urea and plasma electrolytes, serum bilirubin, serum alkaline phosphatase, serum alanine aminotransferase, serum calcium and phosphate, serum uric acid, urinary porphyrins, serum total thyroxine, urinary Bence Jones protein, serum cholesterol and triglycerides, VDRL and TPHA, cold agglutinins, serum cryoglobulins, urinalysis, tissue autoantibody screening, skeletal survey and bone marrow histology. All were normal or negative except for raised triglycerides in Cases 2 and 3 and cryoglobulinaemia in Case 5. Most of these investigations were performed in the remaining 5 cases and were normal or negative except for a weakly positive TPHA and VDRL in Case 10 and the presence of antithyroglobulin antibodies in Case 12. Serum electrophoresis was abnormal in all 12 cases, showing a monoclonal band in the gamma region. These paraproteins were all of μ heavy chain class. The light chain type was κ in 11 cases and λ in Case 9. The paraprotein concentrations are given in Table 1. These levels had been followed for some time in 10 cases (mean 4.2 years, range 1 to 7 years) and remained stable. Serum IgG and IgA were normal in all cases.

The ESR was moderately elevated in 6 cases. The CSF protein content was increased in 10 cases (*see* Table 1). The cell and sugar content were normal. The protein content was estimated several times in Case 1 over ten years and remained stable. In Cases 1, 3, 6, 7 and 12 the proportion of IgG was not elevated (less than 12 per cent). The IgG was 29 per cent of the total protein in Case 2 and 18 per cent in Case 4. CSF electrophoresis on polyacrylamide gel (Thompson *et al.*, 1979) was carried out on specimens from Cases 1 and 12. Both showed abnormalities consistent with a frank transudate of serum proteins. Abnormalities of IgM would not be detected by this system. No other immunological studies were undertaken on the CSF. Serum phytanic acid was normal in Case 6. CT scans were normal in Cases 1, 2, 3 and 12 as were cardiovascular autonomic function tests in Cases 1, 2 and 4.

Neurophysiology

Methods. Ten cases were examined by one of the authors. Unipolar concentric needle electrodes were used for electromyography. Motor conduction velocities and sensory nerve action potentials were measured by standard methods (Gilliatt and Sears, 1958; Thomas *et al.*, 1959; Guiloff and Sherratt, 1977). Further results on these cases were obtained from the records of the Department of Clinical Neurophysiology at the National Hospitals. The remaining 2 cases were studied in the neurophysiological laboratories of other hospitals. F-waves were examined in 4 patients (Cases 1, 5, 6 and 10); recording was from abductor digiti minimi with surface electrodes and nerve stimulation at the wrist.

Results. Electromyographic abnormalities were often present in weak muscles. Fibrillation was sometimes detected, although it was never profuse. Motor unit potentials were commonly large and polyphasic and the recruitment pattern decreased, with surviving units firing at high rates. Complete electrical silence despite full effort or supramaximal shocks to the motor nerve was observed only in the small muscles of the hand or foot. Presumably these muscles were totally denervated.

Motor conduction velocities were reduced, always to less than 50 per cent of the lower limit of normal in at least one peripheral nerve, and frequently in the region of 10 to 20 $m s^{-1}$ in the forearm segments of the median and ulnar nerves. The lowest value found was 3.5 $m s^{-1}$ in the ulnar nerve of Case 11. In 10 cases a velocity was measured in the upper arm segment of the ulnar nerve. The values were similar to those of the forearm segment in 8 patients, but 2 had normal upper arm velocities with marked slowing in the forearm segments (Cases 6 and 10). Distal motor latencies were always prolonged, ranging up to 20 ms from the wrist. Sensory nerve action potentials, both in the upper and lower limbs, were usually absent. Some patients had small delayed potentials in the early stages of the neuropathy but none were detectable a few years after the onset.

F-waves were recorded in 4 patients, the latencies being prolonged (36 to 99 ms, normal less than 32 ms). The latency to deltoid with nerve stimulation at Erb's point was 17 ms in Case 1.

Histology

Methods. Except for Case 8 which was examined elsewhere, segments of nerve obtained at biopsy were fixed for 1 h at 4° C in 3 per cent glutaraldehyde in PIPES buffer (Baur and Stacey, 1977) or in phosphate buffer. After washing in buffer plus 2 per cent glucose they were postfixed in 1 per cent osmium tetroxide in the same solution for 3 h at 4° C. They were then embedded in Araldite *via* 1,2-epoxypropane after dehydration in increasing concentrations of ethanol. Semithin 1 μm sections were stained either with toluidine blue or thionin and acridine orange for light microscopy. Ultrathin sections for electron microscopy were stained with methanolic uranyl acetate and lead citrate and examined with a Siemens Elmiskop 101. Morphometric studies on myelinated fibres were made on photographic montages of the whole transverse area of the biopsy specimen at a magnification of × 1000. Those on unmyelinated axons were made on nonoverlapping photographs of randomly selected areas at a magnification of × 6000.

For the teased fibre studies, a portion of the biopsy specimen was processed as described above, except that postfixation in osmium tetroxide was continued for 24 h and single fibres isolated under a dissecting microscope in unpolymerized Araldite. The fibres were transferred to a glass slide, mounted in Araldite and polymerized in a vacuum oven at 65° C.

Results. Sural nerve biopsies were obtained from Cases 2, 3, 4, 7, 11 and 12 and radial nerve biopsies from Cases 4 and 10. A report on a sural nerve biopsy taken at another hospital was available for Case 8.

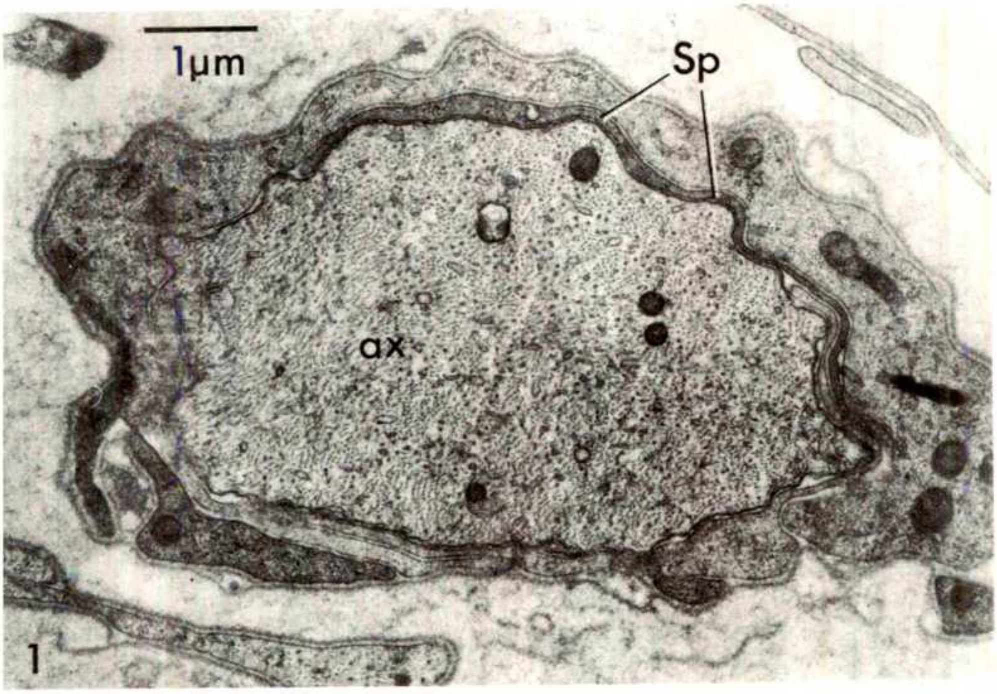
Myelinated nerve fibres. The myelinated nerve fibre population was reduced in all the nerves examined. Quantitative estimates were obtained in Cases 2, 3, 11 and 12. The most severe depletion was observed in Case 3 in which a total sural nerve biopsy was performed. This contained only 36 myelinated nerve fibres in the complete transverse section of the nerve. In Cases 2, 11 and 12, the fibre densities were 2300, 892 and 2666 per mm^2. Myelinated fibres of large calibre were absent from all the biopsy specimens, fibre diameter being consistently less than 8 μm. Control values are given by Thomas (1970) and Behse *et al.* (1972).

Teased fibre studies were undertaken in Cases 2, 3, 7, 10, 11 and 12. In Cases 2, 3 d 11 the myelinated fibres that remained were of such small diameter that lation was not feasible. In Cases 7 and 10 there was evidence of a mixture of gmental demyelination and remyelination, and regeneration after axonal de- neration, Case 12 showing very extensive demyelination and remyelination.

Light and electron microscope studies showed evidence of demyelination and myelination and of axonal degeneration in all the biopsy specimens. Active myelination was seen (fig. 1) and fibres with abnormally thin myelin sheaths for on diameter, indicating remyelination (figs. 2, 3). Concentric Schwann cell oliferation ('onion bulbs') was present in Cases 2, 4, 8, 11 and 12 (figs. 2–5). berrant remyelination was also observed, such as the inclusion of substantial areas Schwann cell cytoplasm containing myelin debris within the myelin sheath (fig. 6).

The myelin of some remyelinated fibres had an abnormal periodicity (fig. 7), with creased separation between the major dense lines (35 nm). This abnormal spacing fected either the outer lamellae of the sheath (fig. 7) or its whole thickness.

Unmyelinated nerve fibres. The density of unmyelinated axons was normal in l cases in which this was examined being 24000, 25239, 40327, 21190 and 4666 per mm^2, respectively, in Cases 2, 3, 8, 11 and 12. The unmyelinated axons ere sometimes related to Schwann cells surrounding remyelinating or regenerating ons (fig. 2).



IG. 1. Electron micrograph (*Case 12*, sural nerve) showing demyelinated axon (ax) surrounded by Schwann cell processes (Sp).

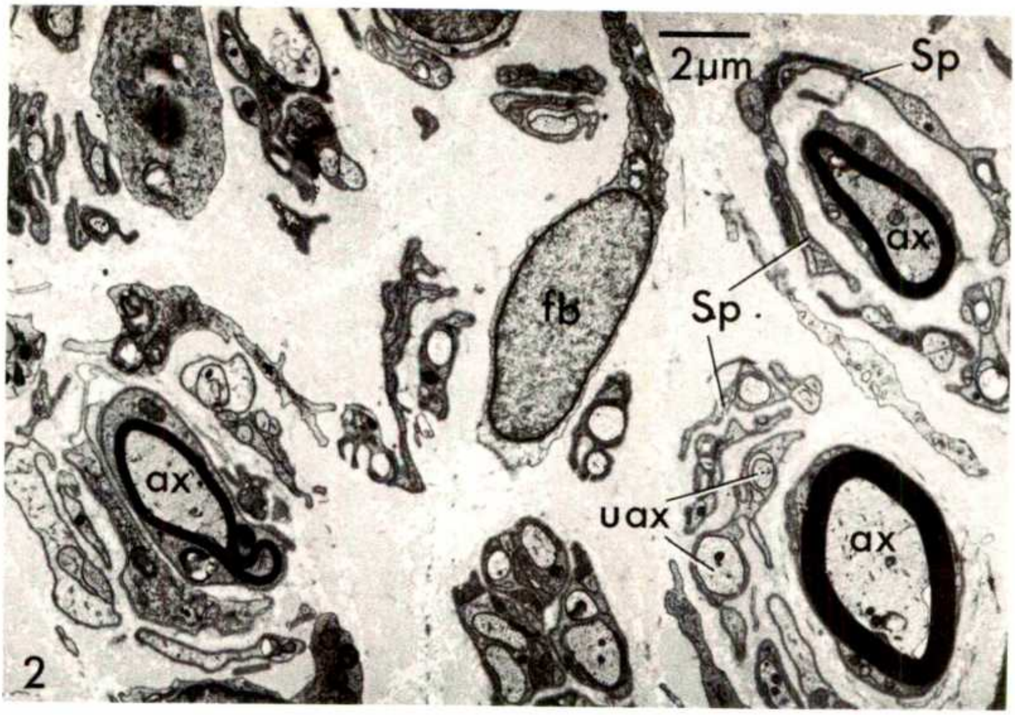


FIG. 2. Electron micrograph (*Case 2*, sural nerve) showing regenerating or remyelinating myelinated axons (ax) surrounded by circumferentially orientated Schwann cell processes (Sp) containing unmyelinated axons (uax); fb = fibroblast.

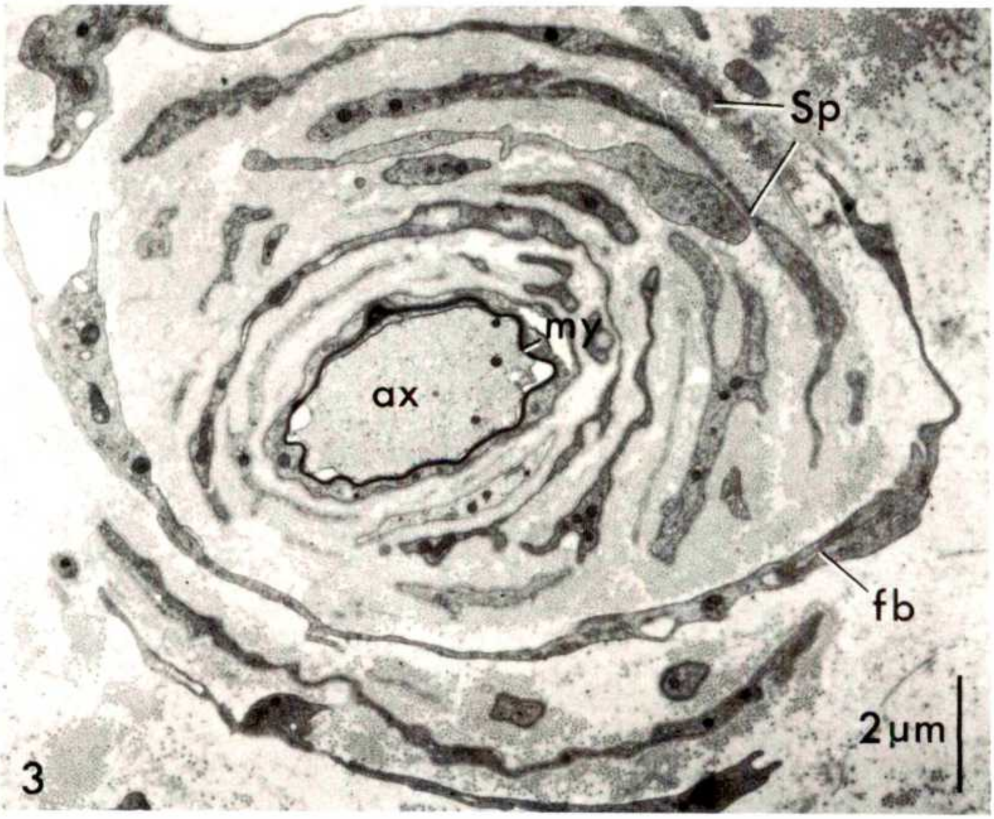


FIG. 3. Electron micrograph (*Case 4*, radial nerve) showing an 'onion bulb'. A central axon (ax) is enveloped by an abnormally thin myelin sheath (my) indicating remyelination. This is surrounded by mutliple circumferentially orientated Schwann cell (Sp) and fibroblast (fb) processes.

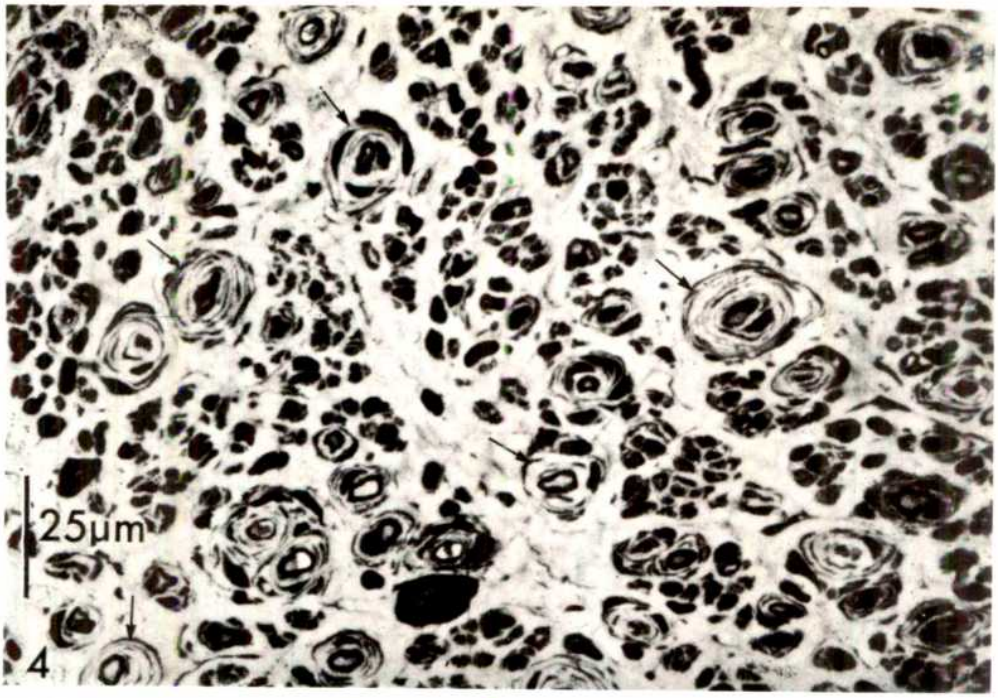


FIG. 4. Transverse section (*Case 11*, sural nerve) showing considerable loss of myelinated fibres and the presence of multiple 'onion bulbs' (arrowed). Semithin section, thionin and acridine orange stain.

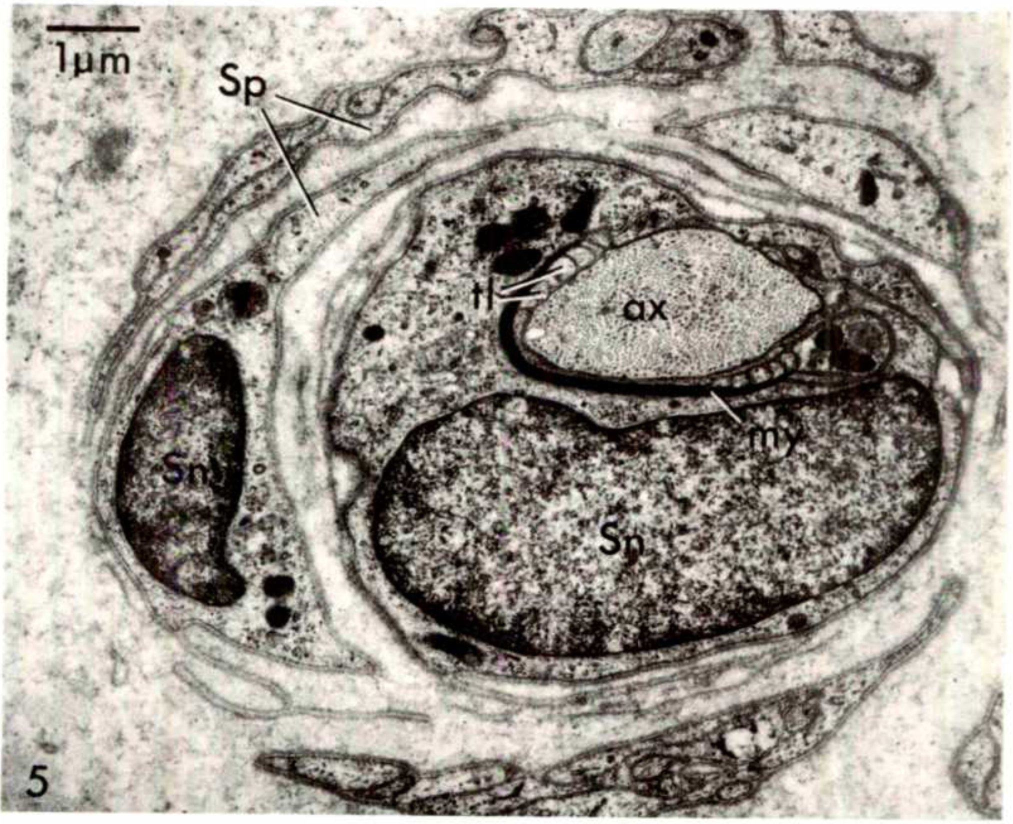


FIG. 5. Electron micrograph (*Case 4*, radial nerve) through a small 'onion bulb'. The axon (ax) is partially surrounded by a thin layer of myelin (my) bearing terminal loops (tl) suggesting proximity to a node of Ranvier. The presence of a nucleus in the associated Schwann cell further suggests that this is a section through a very short intercalated internode. The fibre is surrounded by concentrically arranged Schwann cell processes (Sp). Sn = Schwann cell nucleus.

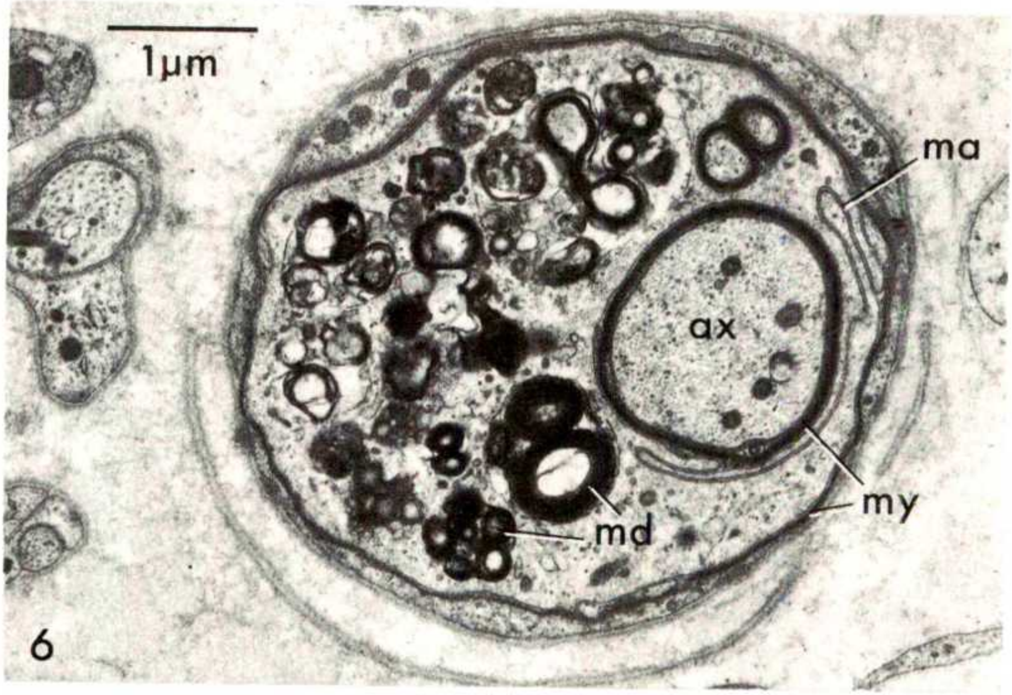


FIG. 6. Electron micrograph (*Case 4*, radial nerve). A small axon (ax) is surrounded by two thin layers of myelin (my) between which there is Schwann cell cytoplasm containing myelin debris (md) and traversed by an 'intermediate' mesaxon (ma).

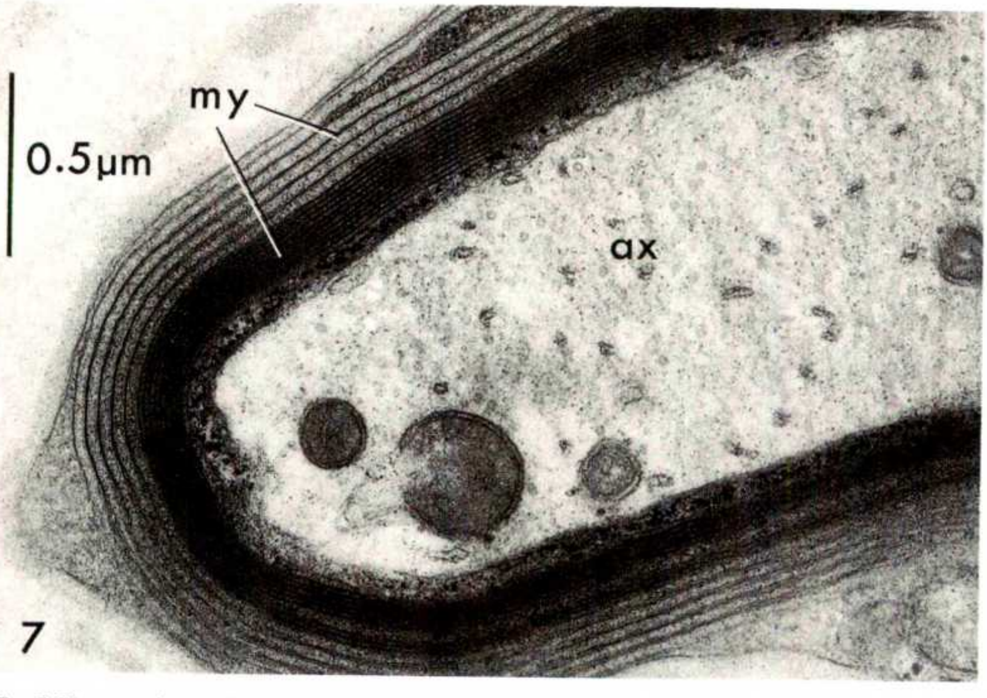


FIG. 7. Electron micrograph (*Case 11*, sural nerve) showing a portion of a myelinated nerve fibre. The axon (ax) is surrounded by myelin (my), the inner lamellae of which have a normal periodicity, whereas in the outer lamellae this is increased to approximately double the normal spacing.

Connective tissues. The amount of endoneurial collagen was increased in most of the nerves examined by electron microscopy (fig. 2). Apart from fibroblasts, the endoneurial spaces contained macrophages, some of which possessed myelin debris, mast cells and occasional small lymphocytes. The endoneurial and subperineurial spaces were frequently expanded and on electron microscopy contained, apart from collagen, granular material and collections of 10 nm filaments (fig. 8). Stains for amyloid were consistently negative. A highly unusual appearance was observed in Case 4, where the endoneurial and subperineurial spaces were filled with multiple vacuoles. Although on electron microscopy many of these vacuoles did not show clearly defined boundaries, they probably arose in the processes of degenerate fibroblasts (fig. 9). A repeat biopsy three years after the first did not show these appearances, but the endoneurial spaces were considerably expanded.

Some perineurial cells were abnormally vacuolated and the perineurial lamellae widely separated by finely granular and fibrillar material (fig. 10). The epineurium and vasa nervorum appeared normal. Endoneurial capillaries were sometimes surrounded by multiple layers of reduplicated basal lamina, but this is a common finding in elderly individuals. No evidence of vasculitis was encountered.

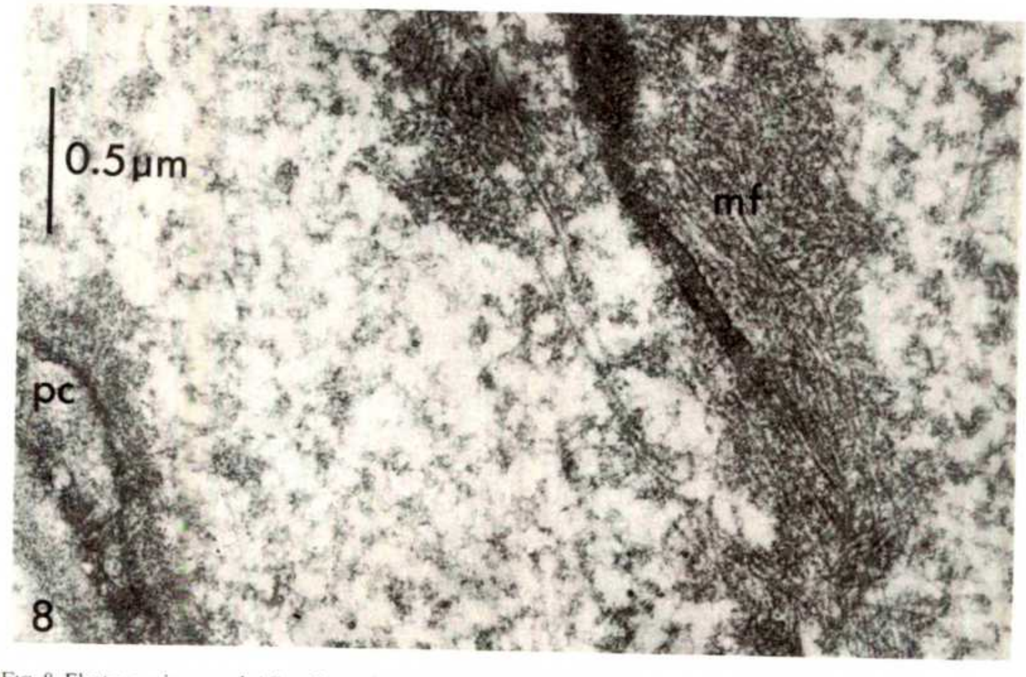


FIG. 8. Electron micrograph (*Case 2*, sural nerve) of subperineurial region, which contains granular material and a collection of microfibrils (mf). To the left of the figure is a portion of a perineurial cell (pc).

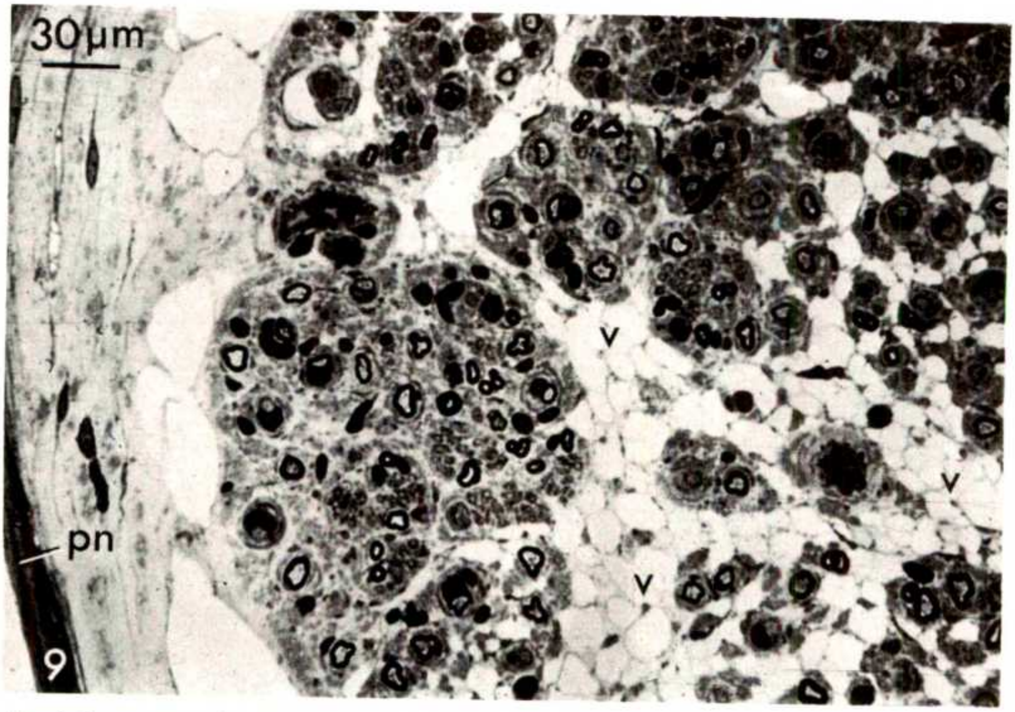


FIG. 9. Transverse section (*Case 4*, radial nerve). The myelinated nerve fibres are generally of small calibre and most are embedded in small 'onion bulbs'. The endoneurial spaces are expanded by multiple vacuoles (v). The perineurium (pn) is to the left of the figure, internal to which is a widened subperineurial space and a number of larger vacuoles. Semithin section, toluidine blue stain.

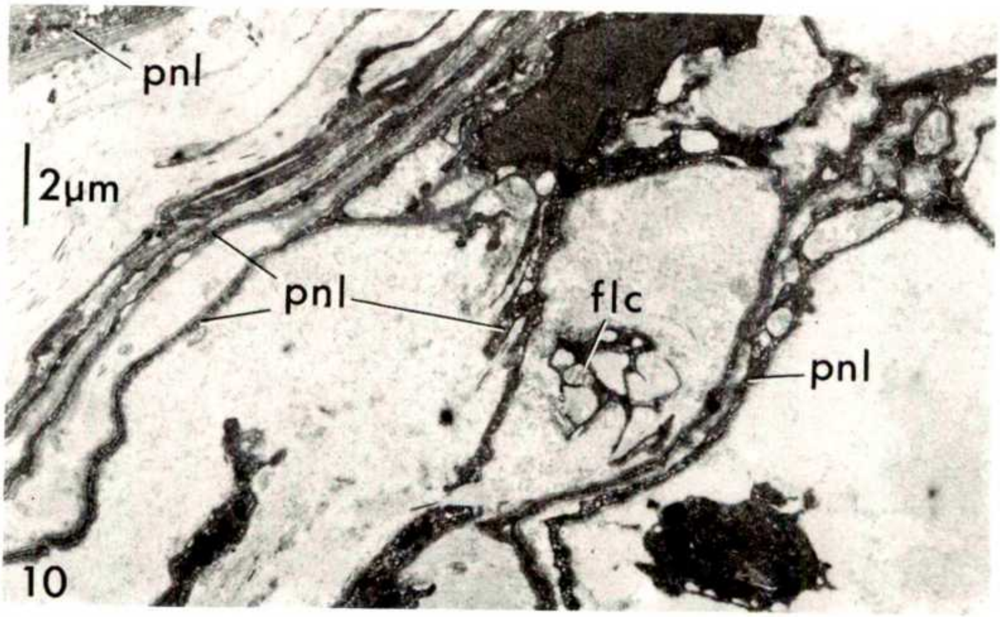


FIG. 10. Electron micrograph (*Case 2*, sural nerve) through perineurium. The perineurial lamellae (pnl) are widely separated. Occasional areas of fibrous long spacing collagen (flc) are visible.

Immunofluorescence and Immunochemistry

Methods. Sera were studied by indirect immunofluorescence for antibodies binding to neural and other tissues from a variety of species. Frozen sections of these tissues, 7 μm in thickness, were air dried, placed in dry acetone for 30 min, followed, when dry, by xylene for 3 min. Sera were diluted 1:5 for initial screening and positive samples were serially diluted until no binding was visible. Antibody titre was recorded as the reciprocal of the last dilution giving positive fluorescence. For the initial screening FITC-conjugated polyvalent antihuman immunoglobulin was used; positive specimens were further studied with antisera specific for heavy and light chains (FITC-conjugated sheep sera specific for human heavy chain classes and unconjugated rabbit antihuman light chain sera followed by FITC-conjugated swine antirabbit immunoglobulin). In recent studies by one of the authors (B.W.L.) it has been found that besides the trout brain or spinal cord, the most selective substrate for detection of a weak antibody to myelin of the specificity of our patients is normal human peripheral nerve cut frozen and fixed with propan-1-ol.

Direct immunofluorescence, performed on sural or radial nerve biopsies from patients or on sural nerves taken at autopsy or from amputated limbs, was carried out on 5 to 7 μm frozen sections, fixed as described above, using antisera specific for human heavy and light chains and complement. The nerve taken from Case 7 was examined by Dr S. Leibowitz using similar methods.

IgM from sera taken from 4 patients was isolated by gel filtration on Sephacryl S-300 after ammonium sulphate precipitation. This gave a preparation contaminated with trace amounts of α_2-macroglobulin. That from Case 11 was subjected to tryptic hydrolysis (Miller and Metzger, 1966). Gel filtration of the digest on Sephadex G-200 resolved peaks corresponding to undigested IgM, F(ab')$_2\mu$, Fabμ and peptide fragments. The F(ab')$_2\mu$ fragment was conjugated with FITC (F : P ratio 2.4). Single layer immunofluorescence using FITC-conjugated F(ab')$_2\mu$ or double layer immunofluorescence using IgM, F(ab')$_2\mu$ or Fabμ followed by FITC-conjugated antihuman μ or κ chain sera, were performed on frozen sections of trout brain prepared as above. This tissue had previously been shown to contain an IgM-binding antigen (*see below*).

Results. Direct immunofluorescence. Nerve biopsies from 8 of the 12 patients were studied by direct immunofluorescence (Cases 1, 2, 4, 7, 8, 9, 11 and 12). The appearances were similar in all cases. There was localization of presumptively monoclonal IgM within nerve fascicles in ring-like formations, which corresponded in number and distribution to the remaining myelin sheaths (fig. 11). There was usually obvious staining for IgM, of varying degree, continuous or discontinuous, in the perineurium. IgG and complement (C3) appeared to be present in small amounts diffusely throughout the fascicles, but were present in larger amounts in epineurium. A similar distribution of IgG has been found in normal nerves and in nerves from patients with a variety of neuropathies (Van Lis and Jennekens 1977). No IgA was detected.

Eight nerves from patients with various peripheral neuropathies unassociated with paraproteinaemia have been examined. A nerve from a patient with cryptogenic axonal neuropathy and IgG paraproteinaemia was also examined. In none of these was IgM detected on any part of the nerve. Similarly none of the 20 nerves taken at autopsy or from amputated limbs has shown any attached IgM.

Indirect immunofluorescence. All 12 patients had serum IgM antibody which bound to human peripheral myelin at titres ranging from 1280 to 5000 (fig. 12). In all cases the myelin-binding antibody was of the same heavy chain class (μ) and light

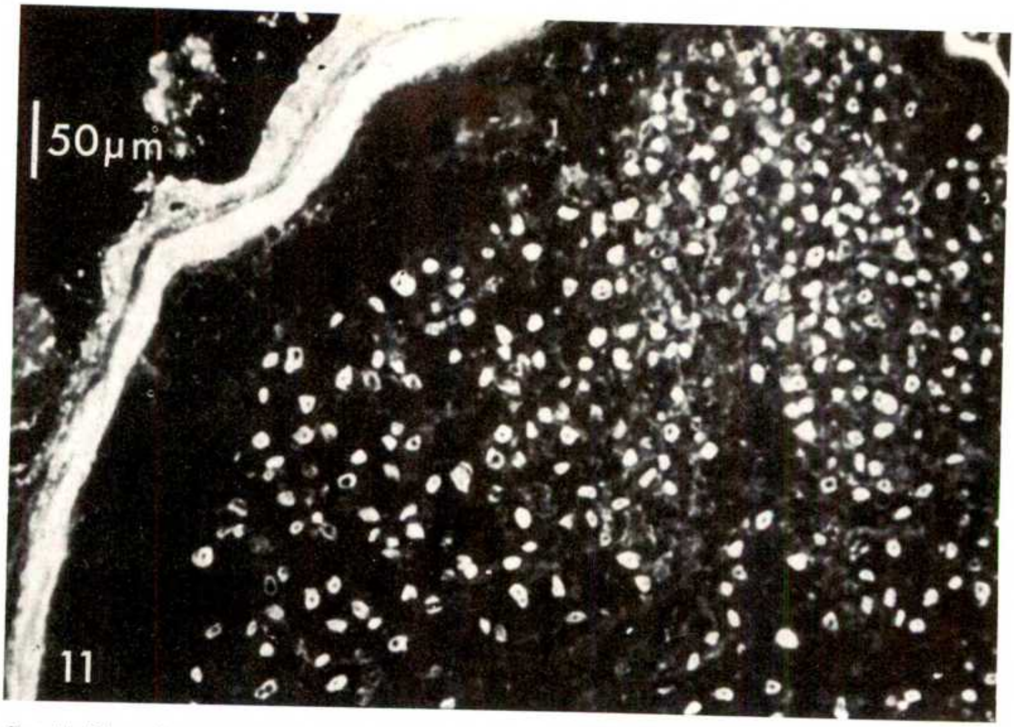


FIG. 11. Photomicrograph under dark ground excitation with blue light of a frozen section of a radial nerve biopsy specimen from *Case 4*. After immersion in acetone for 20 min, drying and exposure to xylene for 3 min, it has been treated with fluorescein conjugated goat antihuman IgM. Note *in vivo* attachment of autologous IgM to surviving myelin sheaths and perineurium. Normal human nerves treated identically showed no fluorescence.

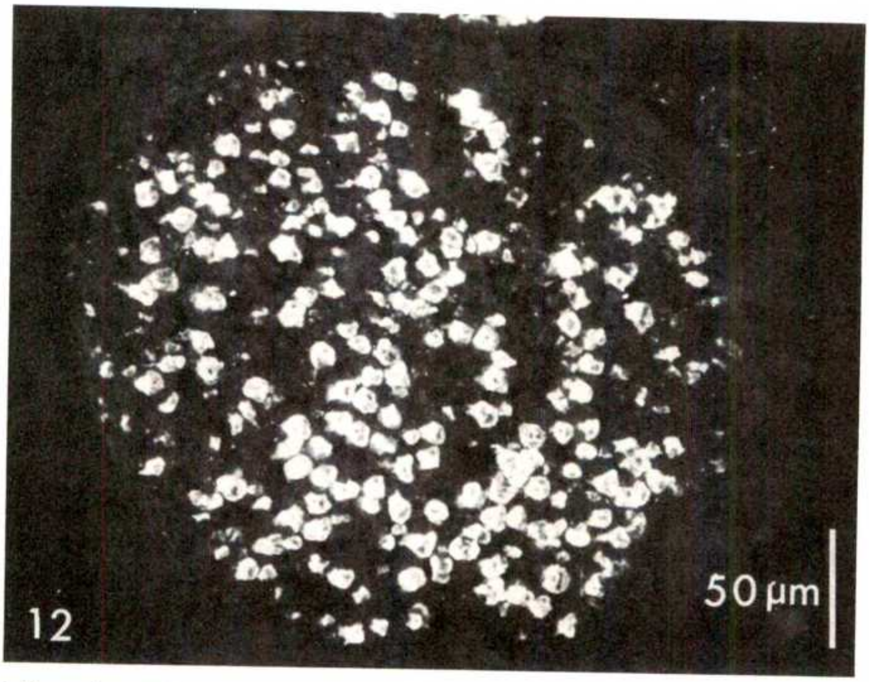


FIG. 12. Photomicrograph under dark ground excitation by blue light of a frozen section of sural nerve from amputated healthy leg of a patient injured in a traffic accident. After immersion in propan-1-ol for 10 min, drying and immersion in xylene for 3 min, it has been exposed to the serum of *Case 11* at a dilution of 1:40 and, after washing, to fluorescein conjugated goat antihuman IgM. Note the attachment of IgM antibody to normal myelin sheaths. Parallel sections treated with normal serum at a dilution of 1:5, but otherwise identically, showed no fluorescence.

chain type as the serum paraprotein, including the one patient with a λ type paraprotein (Case 9).

Thirty-eight of the other 49 patients with benign paraproteinaemia were tested, including all those with peripheral neuropathy. None had myelin-binding antibody of any immunoglobulin class.

The myelin-binding specificity of these monoclonal IgM antibodies was clearly restricted as regards species and site. Thus there were large amounts of antigen present in human and monkey peripheral myelin (fig. 12), but much smaller amounts in human spinal cord myelin and even less in human cerebral and cerebellar myelin. All sera showed strong binding to an antigen present in large amounts in central myelin of teleost fish (trout, goldfish and eel) and somewhat weaker binding in avian (chicken and duck) central myelin. None, with the method of preparation used, showed binding to rat central or peripheral myelin. Sera from 2 patients were tested on a wider variety of species. Both reacted with peripheral myelin of the following animals; cat, dog, chicken, duck, goldfish, eel and trout. There was no significant binding to peripheral or central myelin of any rodent tested (rat, mouse, hamster and gerbil) or the rabbit.

IgM was purified as described from the sera of 4 of the 12 patients, all of whom had IgMκ paraproteinaeima. The purified IgM reacted in Ouchterlony double diffusion with only antihuman μ and κ chain antisera. There was no reaction with antisera against λ light chains or γ heavy chains; 7S IgM was not present. The isolated IgM paraprotein showed the same binding pattern and approximate titre on frozen tissue sections as the corresponding whole sera. The F(ab$'$)$_2\mu$ and Fabμ fragments of the paraprotein from Case 11 gave a binding pattern on trout brain substrate identical to that of the whole serum or purified undigested IgM using FITC-conjugated antihuman μ chain as the second antibody.

DISCUSSION

We have previously reported that there was a disproportionate number of patients with peripheral neuropathy among a group of 56 cases who were referred to a neurological centre and were found incidentally to have benign paraproteinaemia (Kahn *et al.*, 1980). Sixteen cases of neuropathy were encountered. Nine had marked slowing of motor conduction velocity (Group 1). The remaining 7 had known causes of neuropathy or else motor conduction velocities were not significantly reduced (Group 2). The incidence of IgM paraproteinaemia was 29 per cent in Group 2 and 23 per cent in Group 3 which comprised the 40 paraproteinaemic patients without neuropathy (*see* Selection and Clinical Assessment). The other patients in Groups 2 and 3 usually had IgG paraproteins and paraproteinaemia in these groups may have been an incidental finding as the ratio of IgM to IgG paraproteins was similar to that found in cases of paraproteinaemia selected from other hospital populations (Creyssel *et al.*, 1975; Kyle, 1978). However, 7 of the 9 patients in Group 1 had IgM paraproteins (78 per cent). These were the original 7 cases of this report. Five similar cases of IgM paraproteinaemia have been studied since the selection of the first 7.

These 12 cases all had clinical evidence of a peripheral neuropathy and this was substantiated by the neurophysiological and histological investigations. Other recognized causes of neuropathy were excluded. Motor conduction velocities were markedly reduced. Further assessment revealed other common features which suggested that the neuropathies had a similar pathogenesis.

Clinical Observations

All our cases had a chronic sensorimotor neuropathy. There were no particular distinguishing clinical features apart from the prominence of Raynaud's phenomenon and of tremor and ataxia. These movement disorders have been described in various demyelinating neuropathies, for example, the Guillain-Barré syndrome (Haymaker and Kernohan, 1949; Asbury, 1981), chronic relapsing inflammatory neuropathy (Thomas *et al.*, 1969; Matthews *et al.*, 1970; Dalakas and Engel, 1981*a*) and hereditary motor and sensory neuropathy types 1 and 2 (Dyck, 1975; Harding and Thomas, 1980). They also occur in the Miller Fisher syndrome (Fisher, 1956). Fitting *et al.* (1979), Bajada *et al.* (1980), and Spencer and Moench (1980) all described cases of neuropathy and IgM paraproteinaemia associated with ataxia or tremor. The cause of these movement disorders is not known. It has been suggested that they may be related to a disturbance of peripheral sensation, to slowing of nerve conduction in the servomotor loop, or else to an associated disorder of the central nervous system (Adams *et al.*, 1972; Thomas, 1975). C. D. Marsden and J. C. Meadows (unpublished observations reported by Marsden, 1978) found that 7 cases of polyneuropathy with slow motor conduction velocities had dominant tremor peaks smaller than normal physiological tremor peaks and at frequencies not conspicuously different from normal. In our cases, the severity of the tremor or ataxia was not consistently related to the degree of sensory loss (Cases 1 and 2 had marked tremor yet the loss of joint position sense was minimal) nor to the slowing of nerve conduction. The abnormal movements had some of the characteristics of central disorders such as parkinsonism or cerebellar disease, and were often very similar to the abnormalities found in benign essential tremor.

Investigations

Six of the 12 patients had an elevated ESR which showed no tendency to rise with the course of time. The other relevant investigations were negative, there being no evidence of a malignant immunocytic dyscrasia such as myeloma or Waldenström's macroglobulinaemia. The paraprotein levels were followed for a mean of 4.2 years in 10 cases and remained stable. The antithyroglobulin antibody found in Case 12 was of some interest as Blattner *et al.* (1980) described a family in whom several members had Waldenström's macroglobulinaemia and several others had anti-thyroid antibodies. Case 5 had cryoglobulinaemia. That patient had no other features of cryoglobulinaemic neuropathy apart from Raynaud's phenomenon (Logothetis *et al.*, 1968). Propp *et al.* (1975) and Julien *et al.* (1978) found a cryoglobulin in the serum of their cases of IgMκ paraproteinaemia and neuropathy. IgM paraproteins often have the properties of a cryoglobulin (Hobbs *et al.*, 1974).

The CSF protein content was raised in 10 of the 12 cases. This may have reflected pathological changes in the spinal roots. Raised CSF protein has been found in several other cases of neuropathy and benign paraproteinaemia (Thrush, 1970; Latov *et al.*, 1980; Dalakas and Engel, 1981*b*).

Electrophysiology

One criterion for the selection of these patients was slowing of motor nerve conduction velocity to less than 50 per cent of the lower limit of normal in at least one peripheral nerve. This is usually held to indicate the presence of a demyelinating process. Other cases of benign IgM paraproteinaemia and neuropathy have been found to have very slow motor conduction velocities in the range of 15 to 30 m s^{-1} (Swash *et al.*, 1979; Fitting *et al.*, 1979; Dalakas and Engel, 1981*b*). The slowest value found in our patients was 3.5 m s^{-1} in the ulnar nerve of Case 11. Despite this slowing, the compound muscle action potentials, although small, were not greatly dispersed, suggesting that surviving nerve fibres were all uniformly affected. Velocities in the upper arm and forearm were usually similar and the latency in Case 1 from Erb's point to deltoid was 17 ms.

It thus seems likely that the entire length of all motor nerve fibres is involved in a single pathological process. If the underlying abnormality were primary demyelination, the mainly distal distribution of the wasting and weakness presumably implies that associated axonal degeneration is related to the statistical probability of longer fibres being affected by a disturbance that randomly involves fibres from the spinal cord to the periphery. The proportionally smaller loss of shorter fibres might be adequately compensated by collateral sprouting of surviving nerve fibres. This may have accounted for the lack of proximal weakness in these patients.

Histology

The histological studies on the nerve biopsy specimens from the present cases have demonstrated a chronic demyelinating neuropathy with extensive accompanying axonal loss. Myelinated fibres of all sizes are affected. Hypertrophic changes with concentric Schwann cell proliferation were present in half the cases and reflect the chronicity of the process. In the patient with peripheral neuropathy associated with an IgMκ paraproteinaemia reported by Latov *et al.* (1980), extensive demyelination was also demonstrated on sural nerve biopsy, together with numerous 'onion bulbs'. In Case 1 of Swash *et al.* (1979), in which the neuropathy was again associated with an IgMκ paraproteinaemia, sural nerve biopsy revealed changes consistent with a neuropathy predominantly of demyelinating type but without hypertrophic changes.

An interesting feature in the present cases was the presence of uncompacted myelin related to widening of the intraperiod line. This was first demonstrated in paraproteinaemic neuropathy by Sluga (1974) and has been shown to occur in neuropathy accompanying Waldenström's macroglobulinaemia (Propp *et al.*, 1975; Julien *et al.*, 1978; Nardelli *et al.*, 1981) and in chronic relapsing inflammatory neuropathy (P. K. Thomas and R. H. M. King, unpublished). Although the significance of such abnormal myelin spacing is uncertain, similar appearances can be produced in myelinated tissue culture by the application of serum from patients with the Guillain-Barré syndrome (Hirano *et al.*, 1971) or animals with experimental allergic neuritis (Raine and Bornstein, 1979). It would be of interest to establish whether serum from the present patients has the same effect.

Ohnishi and Hirano (1981) have drawn attention to a different type of uncompacted myelin that may be encountered in dysglobulinaemic neuropathy and a number of other conditions in which the inner myelin lamellae are preferentially affected. This form appears to be related to abnormalities in the distribution of the paranodal and adaxonal Schwann cell cytoplasm and was not encountered in the present material.

The unmyelinated fibres appeared to be spared. This was commented upon by Swash *et al.* (1979) and no decrease was found by Latov *et al.* (1980). The density of unmyelinated fibres was normal in each of the present cases in which it was estimated. It is possible that some of the unmyelinated axons counted were regenerating sprouts arising after the degeneration of myelinated fibres, as they were sometimes associated with myelinated fibre regenerative clusters, or with the supernumerary Schwann cells of 'onion bulbs'. This is reminiscent of the aberrant regeneration of myelinated axons that may occur in situations where there is combined degeneration and regeneration of myelinated and unmyelinated axons (King and Thomas, 1971). Nevertheless, it is probable that the sparing of unmyelinated axons is real, as stacks of flattened Schwann cell processes of the type that develop after the degeneration of unmyelinated fibres (Ochoa, 1975) were not an obtrusive feature in these biopsy specimens.

The significance of abnormal vacuolation of endoneurial fibroblasts in Case 5 is uncertain, particularly as this phenomenon was observed in only one instance. The appearances resemble those of the 'giant vacuolated fibroblasts' in type II hereditary sensory neuropathy and hypertrophic neuropathies with a prominent myxoid endoneurial interstitium described by Asbury *et al.* (1971). The endoneurial spaces in our cases were frequently expanded and contained collections of 10 nm filaments. They are similar to those described by Fitting *et al.* (1979) in 3 cases of paraproteinaemic neuropathy where they were thought to resemble amyloid. In our material they did not display the typical 'rigid' appearances of amyloid fibrils and tended to be loosely intertwined with each other. It therefore seems doubtful whether they were amyloid. Neither in our cases, nor in the case of Fitting *et al.* (1979) (who had an IgM paraproteinaemia) in which this was assessed, were stains for amyloid positive.

In the case of peripheral neuropathy associated with a benign IgM paraproteinaemia reported by Forssman *et al.* (1973), a nerve biopsy showed endoneurial lymphocytic infiltrates which were topographically related to deposits of IgM. No axonal or myelin degeneration was detected. In our cases occasional lymphocytes were seen in the endoneurium, but no focal collections were encountered. In addition, there was no evidence of vasculitis.

Immunology

All the nerve biopsies studied by immunofluorescence showed the attachment of monoclonal IgM, presumptively the paraprotein, to the few remaining myelin sheaths. Sera from the 12 cases contained monoclonal antibodies with affinity for human peripheral myelin. The evidence for monoclonality was first the detection of only a single light chain type in association with the μ heavy chain and secondly the correspondence of the heavy chain class and light chain type to that of the circulating paraprotein. Purification and digestion studies have shown that the myelin binding activity in the sera of these patients was a property of the paraproteins themselves. In 11 of the 12 cases the light chain type was κ, perhaps indicating a relationship between the light chain type and the antigenic specificity as suggested for monoclonal cold agglutinin disease by Williams *et al.* (1968).

Examination by one of the authors (B.W.L.) of serum from about 30000 hospital patients over a ten year period, has detected 28 patients with monoclonal myelin-binding antibody, usually of IgM class (9 of these had IgM myeloma, usually of κ type). However, only one has shown a pattern of species and site specificity indistinguishable from that of our patients. This patient had a protracted but undiagnosed illness during which she developed distal sensory symptoms in the limbs which later recovered. The other myelin-binding immunoglobulins, in contrast to the IgM antibodies found in our patients, reacted with neural tissues from a different group of species and usually similarly with both central and peripheral myelin. Variable species specificities of this kind must pose difficulties in elucidating pathogenetic mechanisms by such techniques as intraneural injection of serum. An antimyelin antibody may be strongly reactive with myelin from one species and yet have no reactivity with myelin from another species. This might explain the negative results in one such study (Ansbacher *et al.*, 1981).

There have been several reports of benign IgM paraproteinaemia and peripheral neuropathy, some of which have been reviewed in the Introduction. The 13 cases in these reports are in many ways similar to the ones that we have described. Two nerve biopsies studied by direct immunofluorescence had IgM antibodies localized to surviving myelin sheaths or nerve fibres (Swash *et al.*, 1979; Dalakas and Engel, 1981*b*). Latov *et al.* (1981*a*) found high titres of antimyelin antibodies in the serum of their 4 cases.

The 2 cases of Waldenström's macroglobulinaemia and neuropathy described by Propp *et al.* (1975) and Julien *et al.* (1978) were classified as such because of abnormalities in the bone marrow. Otherwise they were identical to the patients we have described, although Propp *et al.* (1975) did not detect antimyelin antibodies in the serum of their case. Massey *et al.* (1978) and Spencer and Moench (1980) reported 2 cases of neuropathy who were also classified as having Waldenström's macroglobulinaemia on the basis of changes in the bone marrow. These changes were not marked and the cases may have had benign paraproteinaemia. The tremor and ataxia in Spencer and Moench's case were very similar to the movement disorders found in our patients.

IgM binding to peripheral nerve fibres has been found by direct immunofluorescence in the Guillain-Barré syndrome (Luijten and Baart de la Faille-Kuyper, 1972) and chronic relapsing inflammatory neuropathy (Dalakas and Engel, 1980; Nyland *et al.*, 1981). The localization of binding in the former and in the cases of Nyland *et al.* (1981) appeared similar to our results. In those of Dalakas and Engel (1980), it seemed to be to the periphery of myelin sheaths or to the abaxonal portion of the Schwann cell.

Circulating antibodies which bind to neural tissues have been demonstrated in many disorders, for example, the Guillain-Barré syndrome (Melnick, 1963; Tse *et al.*, 1971; Lisak *et al.*, 1975; Nyland and Aarli, 1978; Kennedy and Lisak, 1981), multiple sclerosis (Edgington and Dalessio, 1970; Lisak *et al.*, 1975; Abramsky *et al.*, 1977; Kennedy and Lisak, 1981), carcinomatous neuropathy (Wilkinson, 1964; Wilkinson and Zeromski, 1965), motor neuron disease (Edgington and Dalessio, 1970; Lisak *et al.*, 1975; Kennedy and Lisak, 1981) and Chagas' disease (Khoury *et al.*, 1979). These were usually of IgG class. However, similar antibodies have been found in normal subjects and in patients with various neurological diseases (Allerand and Yahr, 1964; Edgington and Dalessio, 1970; Lisak *et al.*, 1975; Traugott *et al.*, 1979; Kennedy and Lisak, 1981). The nature of the binding of IgG to neural elements may be nonspecific in that it is mediated by Fc-receptors in these neural tissues (Aarli *et al.*, 1975; Traugott *et al.*, 1979), but the same studies indicated that IgM did not appear to bind nonspecifically to myelin. Nonspecific binding *via* the IgM Fc region was excluded in our cases by the demonstrated affinity of Fabμ and F(ab$'$)$_2\mu$ fragments for myelin.

Carter and Lacey (1976) studied sera from 8 patients with macroglobulinaemia and neuropathy by indirect immunofluorescence, and showed that monoclonal IgM from 7 cases bound to axons, glial cells or other neural antigens. A total of 30 out of 53 macroglobulinaemic sera, including 25 from patients with no obvious neurological disorder, also showed similar binding.

Aetiology

Our findings suggest that there is a pathogenetic connection between an IgM paraprotein with affinity for human peripheral myelin and the occurrence of a peripheral neuropathy characterized by the presence of segmental demyelination. It is of course conceivable that the monoclonal antibody may represent an unusual, perhaps genetically determined response to the release of sequestered antigens following nerve damage from another cause. The antibody may then interfere with the process of remyelination. Alternatively, the paraprotein and the neuropathy may not be directly related but both due to the underlying condition (Swash *et al.*, 1979). The immunological studies, however, would appear to us to favour a direct pathogenetic relationship, comparable to that found in chronic cold agglutinin disease in which an IgM paraprotein with affinity for the I antigen on red cell surfaces causes a haemolytic anaemia (Potter, 1971; Hobbs *et al.*, 1974).

Prevalence

The prevalence of this type of neuropathy is low. During six-and-a-half years at a neurological centre only 12 cases have been encountered. In an electrophoretic study of 116 patients with neuropathies of different types, including 33 with idiopathic neuropathies, Nusselt *et al.* (1971) found no significant gammaglobulin abnormalities. This may have been related to the relatively small numbers examined as in a recent prospective study of the prevalence of paraproteinaemia in 270 patients with cryptogenic neuropathy, including those with chronic inflammatory demyelinating neuropathy, 6 per cent had serum paraproteins which were apparently benign (Kelly *et al.*, 1981*b*). The evaluation of any patient with a cryptogenic neuropathy should include serum electrophoresis. It may be that a search for antineural antibodies should be included in such evaluation since some of the monoclonal antimyelin antibodies found by one of the present authors in a general hospital population were not of sufficiently high concentration as to be detectable by electrophoresis or even by immunofixation.

Note added in proof

Since submission of this paper, Braun *et al.* have shown that the antimyelin antibodies reported by Latov *et al.* (1981*a*) react with human myelin-associated glycoprotein (MAG) as judged by the immunoblot technique (Braun P E, Frail D E, Latov N (1982) Myelin-associated glycoprotein is the antigen for a monoclonal IgM in polyneuropathy. *Journal of Neurochemistry*, **39**, 1261–1265).

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SERIAL OBSERVATIONS ON THE PATHOPHYSIOLOGY OF ACUTE STROKE

THE TRANSITION FROM ISCHAEMIA TO INFARCTION AS REFLECTED IN REGIONAL OXYGEN EXTRACTION

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SUMMARY

Regional cerebral blood flow, fractional oxygen extraction and oxygen metabolism have been measured in 34 patients after acute nonhaemorrhagic cerebral hemispheric infarction. Nine cases showed elevated oxygen extraction in the region of the early infarct, and these were the patients studied earliest after the onset of stroke. The results of serial studies to follow the evolution of the pathophysiology of acute stroke in these 9 patients are presented.

The elevated oxygen extraction within the early infarct showed a significant reduction over the week following the onset of stroke. The reason for this fall in the fractional use of available oxygen varied in individual cases, and at the extremes was associated with a marked reduction in oxygen metabolism with a further small fall in residual blood flow, or a return of flow without recovery of oxygen metabolism.

The significance of oxygen extraction in terms of potential viability of the tissue is discussed. The finding of a lower oxygen extraction in subcortical grey and white matter compared to cortex within the first hours or days of a major stroke is considered indicative of an earlier change from ischaemia to infarction in the deep tissues, probably related to the anatomy of the microvasculature.

The interpretation of the results in the light of knowledge accumulated from studies of ischaemia in animals is presented, and problems imposed on data analysis by current limitations in positron emission tomography are discussed.

INTRODUCTION

The assessment of regional cerebral blood flow (rCBF) might seem to be the most important functional measurement in the study of the pathophysiology of nonhaemorrhagic stroke. Techniques designed to measure rCBF in man without exposing the cortex have been available for two decades (Lassen *et al.*, 1963; Glass and Harper, 1963). Although the original methods relied on intracarotid injections of radioactive tracer, refinements now permit noninvasive measurements of cortical rCBF with static external detectors (Veall and Mallett, 1966; Agnoli *et al.*, 1969).

The recent application of single photon emission computed tomography has added a third dimension to the mapping of rCBF (Stokely *et al.*, 1980).

There have been many publications on changes in rCBF after acute stroke in man (for review, *see* Fieschi and Lenzi, 1983). The result of these studies is that much is now known about the altered regulation of flow through an area of brain damaged by ischaemia. It has become apparent, however, that rCBF is a poor indicator of residual tissue function in such circumstances. At the onset of a major reduction in rCBF mitochondrial function remains intact (Schutz *et al.*, 1973; Ginsberg *et al.*, 1977; Rehncrona *et al.*, 1979), which will result in maximal extraction of oxygen (rOER) from the residual trickle of arterial blood. The rate of regional oxygen metabolism (rCMRO$_2$), previously determined by the energy requirements of the tissue, becomes directly dependent upon the residual oxygen delivery. This is the stage of ischaemia, with flow inadequate to meet metabolic demands. After a variable period, depending mainly on the depth and duration of ischaemia, mitochondrial function becomes impaired and rCMRO$_2$ and rOER will fall even if there is no further fall in rCBF. This decline in oxygen uptake, not dictated by a further reduction in oxygen delivery, would be one indicator of impending infarction.

The abnormally low rOER in association with infarction has long been recognized. Feindel and Perot (1965) described 'red cerebral veins' in association with many cerebral lesions, including infarcts, and Lassen (1966) introduced the phrase 'luxury perfusion' specifically to apply to the pathophysiology of cerebral infarction. Both terms describe rCBF disproportionately in excess of rCMRO$_2$, which results in a low rOER and arterialization of the venous blood.

Simultaneous assessments of rCBF and rCMRO$_2$ can therefore give greater understanding of the pathophysiology of stroke than rCBF measurements alone. The ability to study rCBF-rCMRO$_2$ relationships became possible with the application of the oxygen-15 (^{15}O) steady-state inhalational technique to man (Jones *et al.*, 1976; Lenzi *et al.*, 1978). Two-dimensional qualitative imaging has been superseded by positron emission computerized axial tomography (Phelps *et al.*, 1978) which, combined with the ^{15}O technique, gives three-dimensional quantitation of rCBF, rOER and rCMRO$_2$ (Frackowiak *et al.*, 1980). The semiquantitative studies of Baron *et al.* (1978), Ackerman *et al.* (1981) and Baron *et al.* (1981), and the quantitative results of Lenzi *et al.* (1982), have directly demonstrated the uncoupling of rCBF and rCMRO$_2$ in ischaemic or infarcted areas of brain. Ischaemia could be inferred from the pathophysiological pattern of low rCBF, relative preservation of rCMRO$_2$ and high rOER. However, most of the patient studies reported by these authors showed rCBF disproportionately in excess of rCMRO$_2$ within the lesion. rCBF was very variable—high, normal or low—but rCMRO$_2$ was depressed and the 'luxury perfusion' was reflected in the low rOER. These studies were therefore done at a time after the onset of stroke when mitochondrial dysfunction, and in many instances presumably infarction, had become established, and variable reflow had occurred through the region's dysautoregulated vascular bed. Baron *et al.* (1981) observed high rOER in 18 per cent of the cases in their series and commented that it was only present amongst those patients scanned 'early' after the ictus (their earliest study being 30 h).

Although these publications have related patterns of rCBF-rCMRO$_2$ mismatch and absolute levels of rCMRO$_2$ with tissue viability or clinical prognosis, there have been no reports attempting to identify the time after the onset of stroke when ischaemia (potentially reversible) becomes infarction (irreversible). This is of practical importance when planning the timing of therapeutic intervention in early stroke in an attempt to limit the size of eventual infarction.

The changes in rOER after the onset of stroke, taken in the context of the levels of rCMRO$_2$, can be used to infer the transition from ischaemia to infarction, as discussed earlier. This is not to deny that ischaemia is associated with many complex metabolic and structural changes (Siesjö, 1978), nor that it is still not known which of these, once established, is the first to herald inevitable cell death (Siesjö, 1981). However, the attempt to define the period after the onset of stroke when tissue damage remains potentially reversible, using the most appropriate functional measurements available at present that can be made on man, formed the basis of the work that is presented in this paper.

This publication presents serial studies, using positron emission tomography (PET) and the ^{15}O steady-state inhalational technique, on 9 patients with acute, nonhaemorrhagic stroke in whom rOER was observed to be higher in the lesion than in the surrounding brain at the time of the first study. This series was collected by adopting a policy of scanning patients as early after the onset of clinical symptoms as possible. The purpose was to gain insight into the evolution from ischaemia to infarction in man after cerebral artery occlusion, and to determine any difference in the time course of this evolution in cortical grey matter, central grey matter and white matter.

PATIENTS

Patients with acute cerebral hemispheric infarction, diagnosed on clinical grounds, were accepted for quantitative serial studies of rCBF, rOER and rCMRO$_2$. The first study was performed as soon as possible (and no later than 3 days) after the onset of symptoms, the second within one week, and half the cases had a third study three to six weeks later. All patients had a full clinical neurological assessment by one of the authors (R.W.) prior to each study. X-ray transmission CT scanning before, or soon after, the first PET study was used to exclude a primary intra- or extracerebral haemorrhage, or an intracranial tumour, as the cause of the patient's symptoms and signs. All proved to have hemispheric nonhaemorrhagic infarction, two subsequently developing secondary haemorrhage within the infarct demonstrated by further x-ray CT scanning.

A total of 34 patients were studied. Six had internal capsular lesions below the resolution of the PET scanner. Eighteen had more extensive infarction readily apparent on the PET scan, but at the time of the initial study the rOER within the lesion was low. Later studies in this group showed that these infarcts did not subsequently develop an increase of rOER above that of remote, normally perfused cerebrum. Nine patients had a rOER within the lesion that was initially greater than in

TABLE 1. PATIENT DATA

Patient, age, sex	*Presenting signs*	*Timing of PET scans (from onset of stroke)*	*BP mm Hg (at each PET scan)*	*$PaCO_2$ mm Hg (at each PET scan)*	*X-ray CT scan appearances*
P.B.	Global aphasia	3 h	130/75	41	Extensive LMCA territory infarction. Old R temporal cortical infarct
36 M	R h. hemianopia	18 h	140/80	37	
	R hemiparesis	38 days	120/80	41	
G.W.	Global aphasia	7 h	180/100	41	Extensive LMCA territory infarction. Haemorrhage L subcortical grey at 5 days, not present at 6 h
67 M	R h. hemianopia	4 days	160/80	35	
	R hemiparesis	30 days	140/80	41	
J.D.	Global aphasia	24 h	110/70	29	L posterior temporo-parietal infarction
75 M	R h. hemianopia	7 days	120/75	40	
	R hemiparesis				
S.T.	L h. hemianopia	1.5 h	130/90	35	R subcortical grey and white matter infarction
42 F	L hemianaesthesia	7 days	120/70	32	
	L hemiplegia				
O.T.	Global aphasia	8 h	150/80	43	L posterior temporo-parietal infarction
65 F	R h. hemianopia	3 days	130/80	39	
	Minimal R facio-brachial weakness				
E.S.	Global aphasia	−10 days*	180/90	39	Extensive LMCA territory infarction
68 F	R h. hemianopia	7 h	190/95	40	
	R hemiparesis	4 days	160/90	37	
D.L.	Global aphasia	36 h	130/60	33	Extensive LMCA territory infarction
74 F	R h. hemianopia	4 days	145/60	38	
	R hemiparesis	17 days	140/70	37	
L.B.	Global aphasia	3 days	140/90	35	Extensive LACA and LMCA territory infarction
75 F	R h. hemianopia	4 days	Variable†	38	
	R hemiplegia	5 days	Variable†	37	
		39 days	160/85	38	
N.D.	Very drowsy	24 h	180/80	33	Extensive LACA and LMCA territory infarction. Old R cerebral hemispheric infarction
77 F	Anarthric	3 days	120/80	35	
	R hemiparesis				

* First PET study done during the recovery phase of a left cerebral hemispheric TIA, ten days before the onset of a major stroke. † Blood pressure varied by an infusion of angiotensin. LMCA = left middle cerebral artery. LACA = left anterior cerebral artery.

remote cerebrum, and the detailed analysis of the serial studies in these cases forms the subject of this paper. A tenth example has not been included because head movement rendered the second study nonquantitative. Clinical and scanning details about the 9 patients to be discussed are outlined in Table 1. One patient (L.B.) underwent studies during manipulation of systemic blood pressure and as a result was studied four times.

O.T. had pre-existing mixed connective tissue disease and S.T. had sclerodema. Both were on low dose steroids for these conditions and both had pre-existing ischaemic heart disease. Three other patients (P.B., G.W. and J.D.) had ischaemic heart disease, D.L. was a noninsulin dependent diabetic, and E.S. had longstanding hypertension. P.B. and N.D. had x-ray CT scan evidence of old right cerebral hemispheric infarction that had not been suspected before their acute presentations with left hemispheric infarction. L.D. had premonitory left carotid territory transient ischaemic attacks for one month prior to left cerebral hemispheric infarction. All the patients were right-handed.

The purpose and nature of this study has been approved by the Hammersmith Hospital Research Ethics Committee. The United Kingdom Administration of Radioactive Substances Advisory Committee has given permission for the administration of radioisotopes to perform these serial studies. The informed consent of the patient, or where appropriate the informed assent of the nearest relative, was obtained before the commencement of the first study.

METHODS

Data Collection

Tracer theory and positron emission tomography. A patient under study initially inhales tracer amounts of cyclotron-produced ^{15}O-labelled carbon dioxide ($C^{15}O_2$), delivered continuously at a constant rate. Under the influence of carbonic anhydrase in the pulmonary capillary bed ^{15}O is transferred to water ($H_2{}^{15}O$). This labelled 'water of circulation', carried to the brain in the arterial blood, distributes throughout the cerebral tissue. If the patient is left undisturbed to breathe at a steady rate and tidal volume, the regional concentration of isotope in the brain reaches equilibrium after 3 to 5 half lives—the constant delivery of arterial $H_2{}^{15}O$ to the tissues is matched by washout of the tracer and radioactive decay. The short half life of ^{15}O (123 s) prevents the concentration of $H_2{}^{15}O$ ($[H_2{}^{15}O]$) in the tissues attaining that in the arterial blood. However, the higher the rate of flow in a region of brain the closer tissue $[H_2{}^{15}O]$ approaches arterial $[H_2{}^{15}O]$. Therefore at the steady-state during $C^{15}O_2$ inhalation tissue $[H_2{}^{15}O]$ is related to rCBF.

The patient then inhales ^{15}O-labelled molecular oxygen ($^{15}O_2$); $^{15}O_2$, bound to haemoglobin, reaches the brain, is extracted by aerobically respiring cells, and is rapidly converted to '$H_2{}^{15}O$ of metabolism'. At the steady-state during $^{15}O_2$ inhalation regional tissue $[H_2{}^{15}O]$ is proportional to rCBF × rOER (as arterial $[^{15}O_2]$ is constant). rOER is therefore proportional to the ratio of regional tissue $[H_2{}^{15}O]$ during $^{15}O_2$ inhalation to regional tissue $[H_2{}^{15}O]$ during $C^{15}O_2$ inhalation.

If regional tissue $[H_2{}^{15}O]$ is known and plasma and arterial $[H_2{}^{15}O]$ are measured, then simple tracer equations may be solved for rCBF (in absolute units) and rOER (Frackowiak *et al.*, 1980). The term for rOER takes into account $H_2{}^{15}O$ present as recirculating labelled water washed out from the aerobically respiring tissues of the body. $rCMRO_2$ can then be derived (in absolute units) from the relationship:

$$rCMRO_2 = rCBF \times rOER \times \text{total stable oxygen content of arterial blood}$$

Regional tissue $H_2{}^{15}O$ activity is measured by PET. The decay of a positron-emitting isotope is accompanied by the release of oppositely directed gamma rays. These annihilation photons are recorded by a ring of paired detectors and, using standard tomographic data collection and reconstruction, the distribution of ^{15}O within a chosen plane is visualized. The tomograph is designed to respond linearly over the range of isotope concentrations encountered in patient studies and therefore, if attenuation of the signal by brain and skull is corrected for, absolute regional $[H_2{}^{15}O]$ is measured. Arterial blood samples taken during the steady-state of both the $C^{15}O_2$ and $^{15}O_2$ inhalational periods are used to measure $H_2{}^{15}O$ activity in plasma and whole blood in a well counter cross-calibrated with the tomograph.

The use of the ^{15}O steady-state technique with PET has been subjected to a rigorous theoretical and statistical analysis (Lammertsma *et al.*, 1981, 1982). These authors demonstrate the error in rOER estimation that occurs when no allowance is made for the superimposition of signal from the blood $^{15}O_2$ and $H_2{}^{15}O$ on signal from the tissue $H_2{}^{15}O$, resulting in overestimation of tissue $[H_2{}^{15}O]$. It is possible to correct for the signal from the blood pool by determining the regional cerebral blood volume (rCBV) and incorporating this value in the tracer equation (*see* Lammertsma *et al.*, 1981). rCBV is measured by delivery of a bolus of a tracer amount of carbon-11 monoxide (^{11}CO) to the patient (^{11}C is a positron-emitting isotope with a half-life of about 20 min). ^{11}CO binds to haemoglobin and remains in the blood pool and its distribution in the brain is measured with PET.

If the activity of ^{11}C in a venous blood sample is also measured it is a simple matter to derive rCBV (Phelps *et al.*, 1979).

Scanning procedure. Patients were scanned on an ECAT II (EG and G Ortec, Oak Ridge, Tennessee) PET scanner, using the medium resolution shadow shields to give a transaxial resolution of 16 × 16 mm (full width half maximum, FWHM) and a slice thickness of 16 mm (FWHM). The patient's head was positioned on a head rest and a grid of light was projected on to the patient's forehead and aligned with washable ink marks. Any movement of the patient's head was then immediately apparent and very accurate repositioning was possible. The head was aligned with the orbitomeatal (OM) line parallel to the plane of the ring of detectors and the patient couch moved to scan any chosen plane above the OM line. Careful attention was paid to positioning the patient's head before each study to scan the same planes each time.

A face mask delivered cyclotron-produced $^{15}O_2$, $C^{15}O_2$ and ^{11}CO sequentially to the patient at carefully controlled rates. Arterial sampling was obtained either *via* a short, 21-gauge Teflon, radial artery cannula, or by direct puncture of the radial or femoral artery. The radial artery cannula was inserted prior to the study, after Allan's test had confirmed adequate collateral flow in the ulnar artery. Radial artery cannulation had the advantage that several samples during each steady-state could be taken to ensure that stability of arterial [^{15}O] had been achieved. Monitoring of head activity by an external detector was used as a check on the stability of head counts during the scanning period.

The method of collection of emission data during $C^{15}O_2$ and $^{15}O_2$ inhalation, and its correction for attenuation of positron annihilation photons at each point in a plane by means of a transmission scan using an external ring source of ^{68}Ge, has been described previously by Frackowiak *et al.* (1980). Arterial whole blood and plasma ^{15}O activity, haematocrit, PO_2, PCO_2 and pH, and haemoglobin were also measured by the same methods used by these authors. Emission data to determine rCBV was collected after the patient had inhaled tracer amounts of ^{11}CO for a short period. After 5 min had elapsed from the end of inhalation to allow equilibration, a maximum of two planes were scanned for 5 min each. Whole blood ^{11}C activity was measured to permit quantitation of rCBV.

Data analysis

Two methods were employed.

1. Cortical plots placed on computer printouts of the functional data.
2. Regions of interest placed on images of the functional data displayed on the computer visual display unit.

Cortical plots. A computer printout was obtained for regional values of CBF, $CMRO_2$ and OER. Each number in the numerical matrix represented the mean value of 3 × 3 picture elements (pixels), that is, an area of brain in the transaxial plane of 0.75×0.75 cm^2. The pairs of numbers with the highest values near the edge of the numerical matrix of the $CMRO_2$ data were identified. The mean of each pair was taken to represent the $CMRO_2$ of a region of cortical grey matter, plus a variable amount of white matter and subarachnoid space, measuring 1.5×0.75 cm^2 in the transaxial plane; 20 to 25 such pairs encompassed the cortex of each hemisphere. The cortical strips defined on the $CMRO_2$ matrices were placed on those of OER and CBF to obtain these values from congruent regions. Fig. 1 shows the CBF, OER and $CMRO_2$ images at 4 and 6 cm above the OM line of a normal volunteer and the identification of the 'cortex' on the $CMRO_2$ matrices.

The cortical strip was divided into anatomical regions and, by choosing regions of similar length and position from the various studies of one patient, the mean serial values of rCBF, rOER and $rCMRO_2$ for the segment of cortex selected could be compared. Typically, strips of cortex 2.3 cm long were chosen at the anterior and posterior margins of an infarct and 3.0 to 5.3 cm (depending on the size of the infarct) at the centre. These could be compared with mirror regions of cortex in

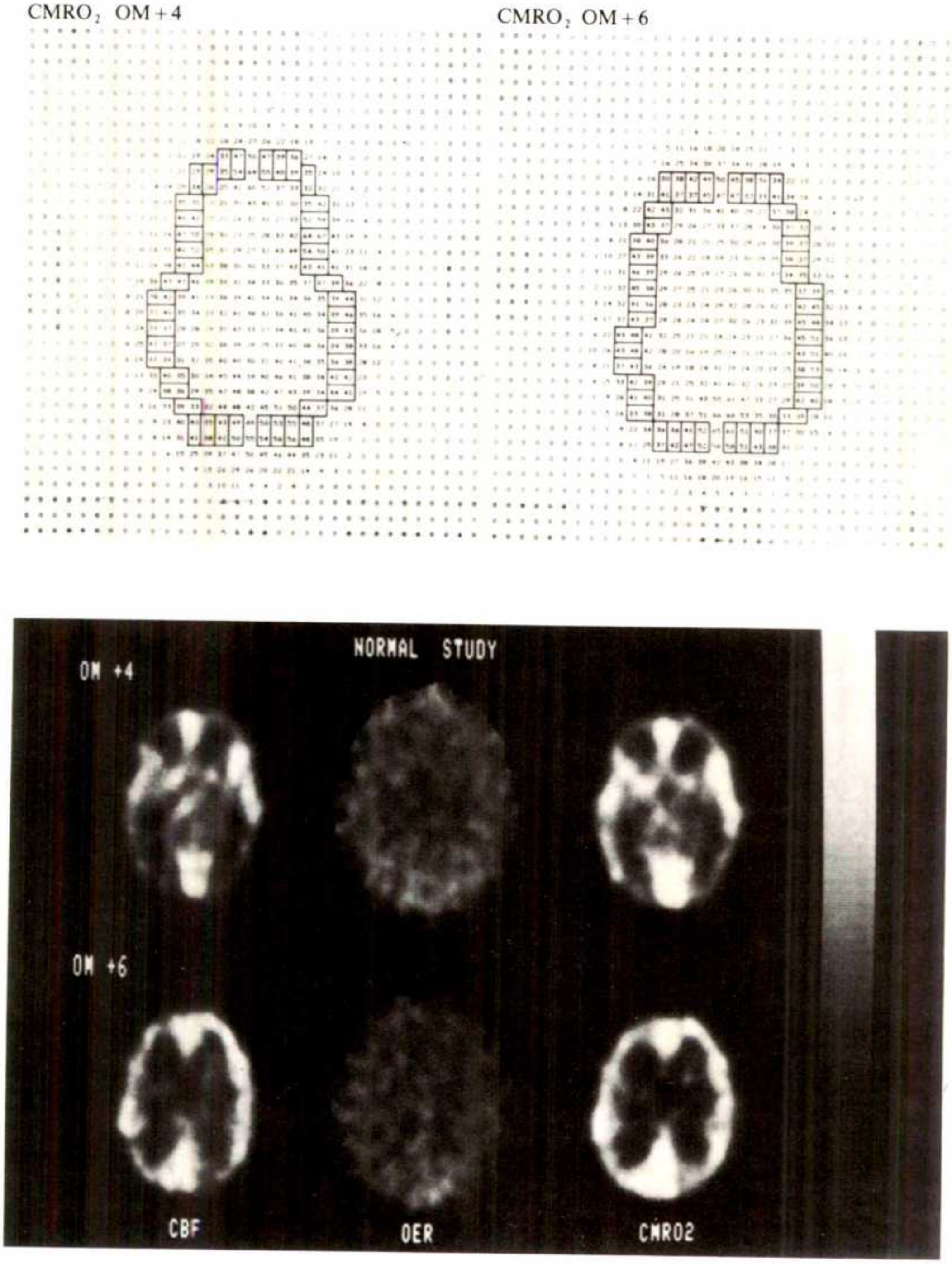


FIG. 1. Data analysis on the numerical matrix of the data. The functional images of CBF, OER and CMRO$_2$ in a normal volunteer, at 4 and 6 cm above the OM line, are depicted below. Above is shown the 'cortex' on the CMRO$_2$ numerical matrices at the two levels, identified by the method described in the text.

the contralateral hemisphere. An alternative method of presenting the data was to plot the mean value of the paired numbers defining the cortex against the distance around the cortex.

Regions of interest. The functional data were displayed as images on the computer's visual display unit, and circular or oval regions of interest were constructed on the images using a standard Ortec computer software programme. This method of data analysis was used to obtain values of $CMRO_2$, CBF and OER for subcortical grey matter (the lentiform and thalamic nuclei) and subcortical white matter. Once a region had been identified on the $CMRO_2$ scan image the computer printed out the mean values of $CMRO_2$, CBF and OER for this chosen area. The smallest area used for a region of interest was 2.6 cm^2, and the narrowest diameter of an oval region 1.5 cm.

A problem with data analysis was that the resolution of the scanner imposes an uncertainty about the measured values within a chosen region of brain compared to the true values. The larger the region that is sampled the less this uncertainty becomes. An area twice the resolution of the scanner gives total recovery of radioactive counts (Hoffman *et al.*, 1979) and represents a minimum 'optimum' size for regional analysis of the data. The chosen minimum width for defining the cortex on the cortical plots, and the minimum size of the regions of interest used to obtain the functional data from subcortical structures, were chosen as the best compromise between the physical dimensions of the anatomical elements of the brain and the resolution of the ECAT II scanner.

RESULTS

The concept that at the onset of severe partial ischaemia rOER is elevated, with $rCMRO_2$ preserved relative to rCBF, was presented in the Introduction. The initial search for elevated rOER in patients studied within three days of the onset of stroke revealed this pathophysiological pattern in only 10 of a total of 28 cases with lesions within the resolution of the scanner (*see* earlier section on the selection of patients). Analysis of the timing of the first PET study in all 28 patients revealed that the 10 with high rOER had, overall, been those studied earliest after the onset of stroke (*see* Table 2). The only study done within 12 h of the ictus not to show a high rOER was in a patient with a very severe reduction of rCBF (< 5 ml/100 ml/min) and $rCMRO_2$ (< 0.5 ml/100 ml/min) throughout the left middle cerebral artery territory, and this was an extension of a previous, smaller infarct. In the 14 cases with the first study delayed until after 24 h from the ictus, 12 showed a low rOER within the lesion.

The initial hypothesis arising from these single early observations is that rOER is only transiently elevated, and this stage had been missed in the 18 patients with low rOER. Confirmation of this hypothesis, and the pathophysiological changes underlying the change from high to low rOER, required the quantitative serial studies available on 9 of the 10 patients with elevation of rOER at the first study.

TABLE 2. TIME INTERVAL BETWEEN THE ONSET OF SYMTOMS AND THE FIRST PET STUDY ON EACH PATIENT, RELATED TO THE PRESENCE OF HIGH OR LOW rOER WITHIN THE LESION

Time intervals (h)	0–12	12–24	24–48	48–72
No. with high rOER	5	3	1	1
No. with low rOER	1	5	6	6
Total	6	8	7	7

The serial results in one patient (E.S.) will be presented to demonstrate the detailed consideration of the evolution of pathophysiological changes that was possible from individual patient studies. The overall results of the serial studies, and then the functional consequences of manipulation of systemic blood pressure in L.B., follow. The clinical findings in relation to the observed pathophysiological changes conclude this Results section. All values for rOER (and $rCMRO_2$) are corrected for rCBV unless otherwise stated.

Serial Changes in rOER, and the Underlying Alterations in rCBF and $rCMRO_2$, in Early Cerebral Infarcts

Patient E.S. was first studied during the recovery phase of a transient ischaemic attack in the left middle cerebral artery territory. The study, done 8 h after the onset of symptoms, did not reveal a deficit of either rCBF or $rCMRO_2$. Ten days later E.S. had a completed stroke, with global aphasia and right hemiparesis. Two further PET studies, 7 h and four days after the ictus, were done. Values of CBF and $CMRO_2$ from the left posterior frontal/anterior temporal cortical strip (3.8 cm long), the superficial central area of the infarct, were compared with those from the anterior and posterior adjacent areas of cortex (each 2.3 cm long) which formed the margins of the infarct. Further comparison was made with the changes in CBF and $CMRO_2$ in the region of the left lentiform nucleus.

Fig. 2 displays the scan images at the relevant plane from the three studies and fig. 3 shows the quantitative data plotted as $CMRO_2$ against CBF. The slope of the relationship between $CMRO_2$ and CBF is the OER, and therefore disproportionate changes in CBF and $CMRO_2$ are accompanied by changes in OER. More strictly, when comparing $CMRO_2$ and CBF measured on several occasions, the slope of $CMRO_2$ against CBF represents arteriovenous oxygen difference ($A\text{-}VDO_2$), and OER is only related to the $A\text{-}VDO_2$ for all the studies if the total stable oxygen content (O_2C) of the arterial blood has not varied (as $CMRO_2 = CBF \times A\text{-}VDO_2$, and $A\text{-}VDO_2 = OER \times O_2C$). The O_2C was very similar for all three studies on E.S. (20.1 ± 1.0 ml/100 ml).

The fall in cortical rCBF in left middle cerebral artery territory 7 h after the major stroke, compared with the same region's CBF ten days previously, is readily apparent, but $rCMRO_2$ remained relatively preserved and rOER was increased. At the same stage the region of the lentiform nucleus showed a greater depression of rCBF and $rCMRO_2$ than the overlying cortex. By four days the cortical centre of the early infarct showed a further fall in CBF, but rOER had decreased because of a large reduction in $rCMRO_2$. rOER also fell at the cortical margins of the infarct, more anteriorly than posteriorly, in response to only minor changes in rCBF and $rCMRO_2$. The lentiform nucleus at four days showed a further reduction in a previously severely depressed $rCMRO_2$.

A fall in rOER in the cortical centre of the infarct, over the interval between the first and second studies, was seen in 8 of the 9 cases in this series. A strip of cortex with the highest rOER was defined in one plane of the ischaemic hemisphere

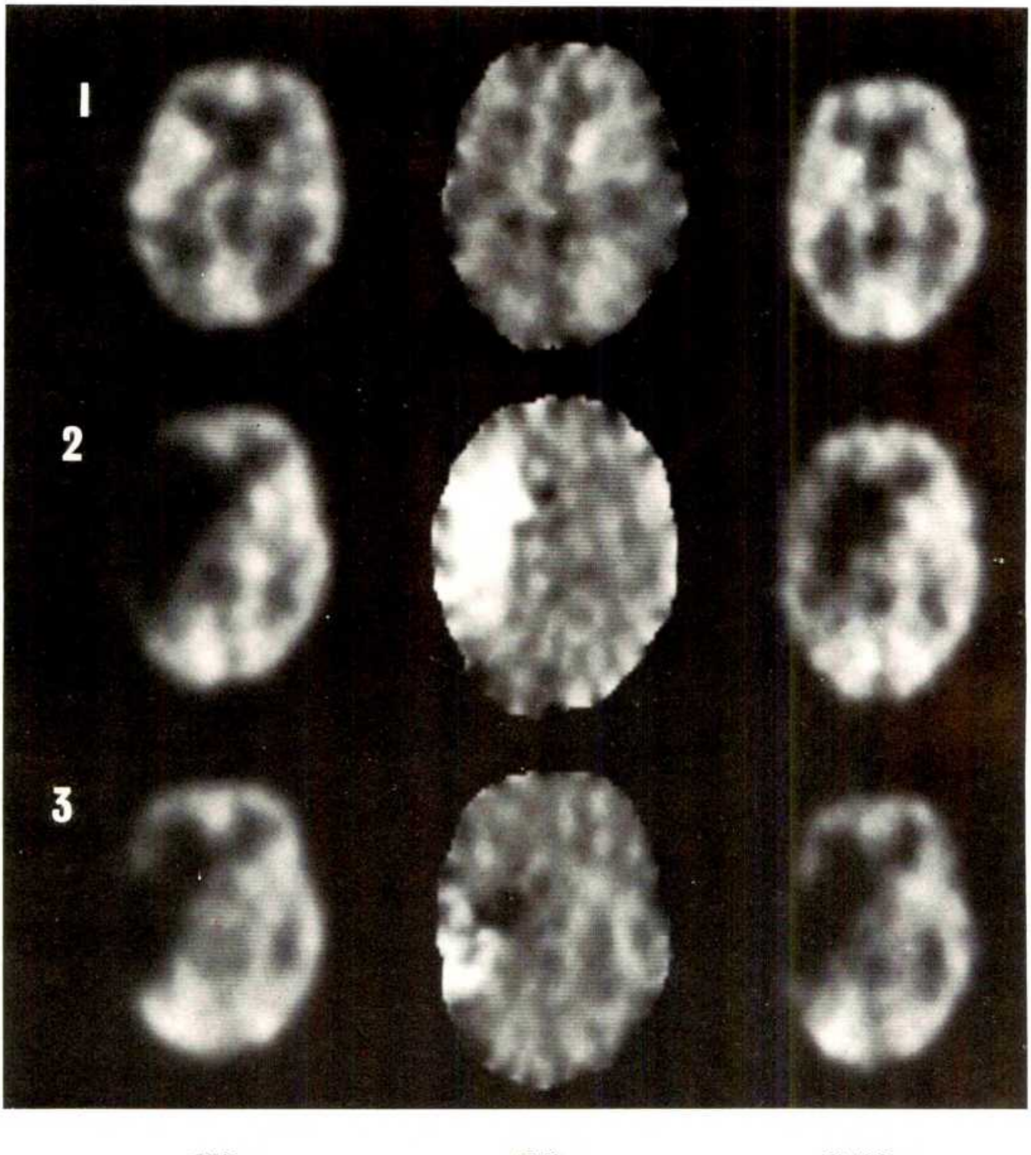


FIG. 2. Functional images of the three studies on patient E.S. at OM + 4.5 cm. The CBF images are on the left, OER in the middle and $CMRO_2$ on the right. Study 1 (1) was done after a left hemisphere TIA, study 2 (2) 7 h after a major stroke ten days later, and study 3 (3) four days after the stroke. The high rOER within the early infarct observed at the time of study 2 fell in association with a decline in cortical $rCMRO_2$ by study 3.

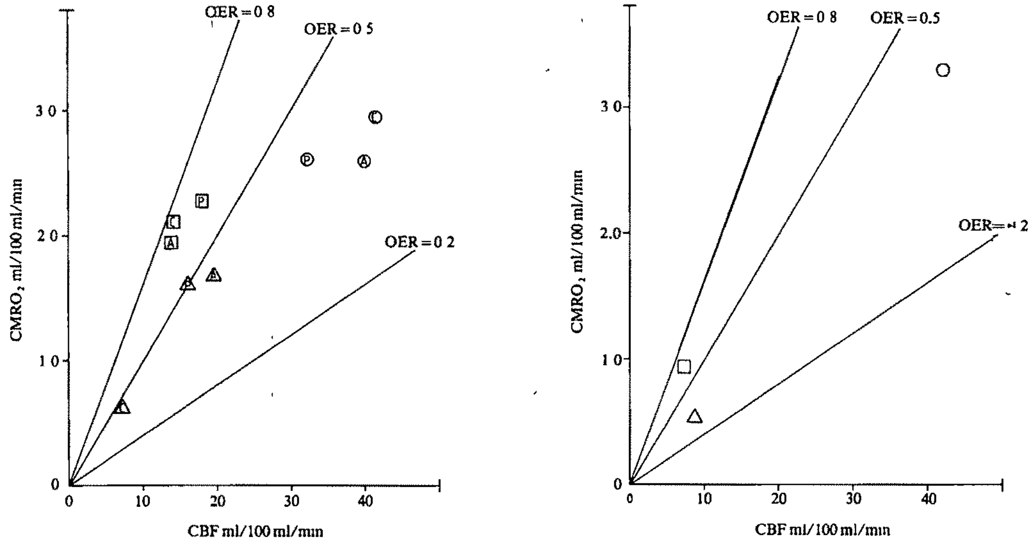


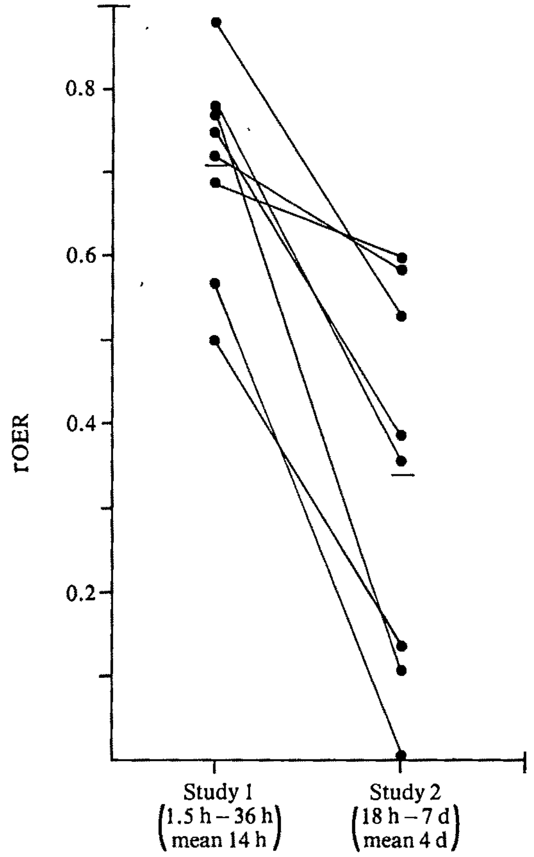
FIG. 3. $CMRO_2$-CBF plots of the changes within regions of the left hemisphere, at OM+4.5 cm, in the three studies on patient E.S. Changes in the cortex are shown on the *left*, and in the subcortical grey matter (predominantly lentiform nucleus) on the *right*. A = anterior edge of infarct. C = centre of infarct. P = posterior edge of infarct. ○ = study 1. □ = study 2. △ = study 3.

from the first PET study of these 8 cases. The cortical regions all came from the centre of the lesions, rather than the margins, as judged by the degree of depression of rCBF—the cortex with the highest rOER also had the lowest rCBF. Identically situated cortical regions were identified in the second studies. The change in cortical rOER between the first and second studies in these 8 patients is shown in fig. 4. In all cases there was a fall in rOER, with a mean of 0.71 ± 0.12 for the first study and 0.34 ± 0.23 for the second, and this difference was significant ($2P < 0.005$). The time of the first study varied between 1.5 and 36 h (mean 14 h) after the ictus, and the second 18 h to 7 days (mean 4 days).

Fig. 5 shows the changes in $rCMRO_2$ and rCBF in these same cortical regions over the interval between the first and second studies. In 2 patients there had been a further fall in rCBF, but a proportionately much greater fall in $rCMRO_2$ (60 to 80 per cent). One patient had an obvious extension of the initial infarct (apparent both on serial x-ray CT scans and the PET scans, although not apparent clinically) and both rCBF and $rCMRO_2$ fell to immeasurably low levels by three days. Three patients showed a large increase in rCBF (50 to 300 per cent), associated with a small decrease in $rCMRO_2$. Two patients had relatively small degrees of reflow (increases in rCBF of 35 per cent), accompanied in one by a 20 per cent increase in $rCMRO_2$.

In summary, flow in relation to oxidative metabolic demands increased early in the region of infarction in 8 of the 9 cases. However, this uniform fall in rOER

FIG. 4. Changes in cortical rOER within the infarct between the first and second studies in 8 of the 9 cases. The fall in mean rOER is significant ($P < 0.005$) * t-test for two-tailed unpaired differences.



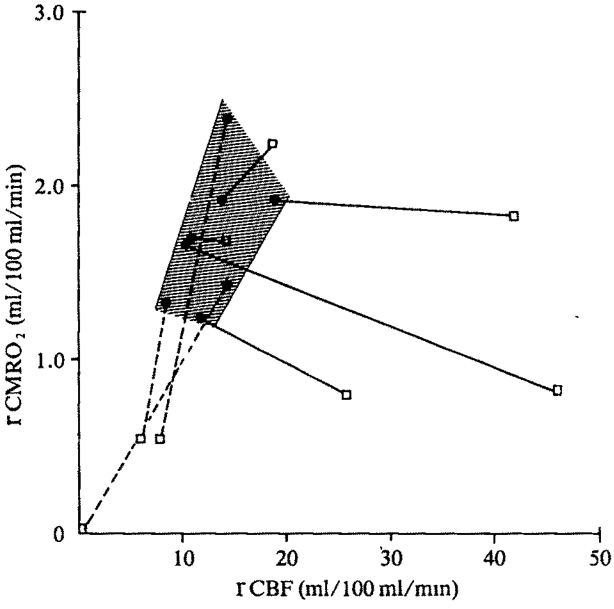


FIG 5 Changes in $rCMRO_2$ and rCBF underlying the fall in cortical rOER between the first and second studies shown in fig. 4. The cortical $CMRO_2$-CBF relationships within the infarcts at the time of the first studies on the 8 patients lie within the shaded area. Changes accompanied by a further decrease in rCBF are represented by broken lines, and those with increases in rCBF by continuous lines. ● = study 1 (1.5 h to 36 h, mean 14 h). □ = study 2 (18 h to 7 days, mean 4 days).

TABLE 3. MEAN rCBF, rCMRO$_2$ AND rOER IN THE ANTERIOR CORTICAL MARGIN OF THE INFARCTED REGION. COMPARISON BETWEEN THE FIRST AND SECOND STUDIES

	rCBF (ml/100 ml/min)	*rCMRO$_2$ (ml/100 ml/min)*	*rOER*
1st study	21.2± 5.0	2.1±0.4	0.54±0.09
2nd study	29.4±10.0	2.0±0.4	0.43±0.16
n = 7*	*P* n.s.*	*P* n.s.**	*P* n.s.**

* Patient N.D. has been excluded because of obvious extension of the infarcted area between first and second studies. ** t-test for two-tailed unpaired differences.

was secondary to very different individual changes in rCBF and rCMRO$_2$, which could be broadly categorized into two patterns: either a further fall in both rCMRO$_2$ and rCBF, or variable reflow with little change in rCMRO$_2$.

The anterior and posterior cortical margins of the infarct in the 7 patients without apparent extension of the area of infarction had small changes in rCBF, rOER and rCMRO$_2$ between the first and second studies that were not significant. Table 3 summarizes the mean changes in the anterior margins (those in the posterior margins were very similar). None of these cases showed evidence, within the resolution of the scanner, of a rim of persistently elevated rOER around the edge of the infarct.

The changes in the cortex affected by ischaemia were not accompanied by changes in the mirror cortex of the contralateral hemisphere, summarized in Table 4.

Mean blood pressure and arterial PCO$_2$ did not change significantly between the two studies in the 8 patients (BP 150±30/85±15, PCO$_2$ 37±5 torr during the first study; BP 140±20/75±10, PCO$_2$ 37±3 torr during the second). However, in one patient (N.D.) there was a fall in systolic blood pressure of 60 torr between the two studies, and this was accompanied by a large extension of the left hemisphere infarct during this period. Another patient (J.D.) had clinically observed, continuous hyperventilation during the first study at 24 h, associated with an arterial PCO$_2$ of 29 torr, and a normal arterial PCO$_2$ of 40 torr during the second study at seven days. The cortex remote from ischaemic injury showed normal vasomotor reactivity

TABLE 4 MEAN rCBF, rCMRO$_2$ AND rOER IN THE MIRROR CORTEX OF THE CONTRALATERAL HEMISPHERE COMPARISON BETWEEN THE FIRST AND SECOND STUDIES

	rCBF (ml/100 ml/min)	*rCMRO$_2$ (ml/100 ml/min)*	*rOER*
1st Study	36.7±9 3	2.8±0.4	0.43±0.10
2nd Study	42.4±7 6	3.0±0.5	0.41±0.08
n = 6*	*P* n.s **	*P* n.s.**	*P* n.s.**

* Patients P.B and N.D. have been excluded because x-ray CT scans showed old infarction in the mirror cortex of the contralateral hemisphere ** t-test for two-tailed unpaired differences.

in response to the change in arterial pCO_2 (rCBF almost doubled), with no change (< 10 per cent) in $rCMRO_2$. The area of infarction in the left parietal region showed good reflow between one and seven days after the ictus (rCBF increased fourfold) but $rCMRO_2$ declined from 1.8 to 0.9 ml/100 ml/min. Although there was no evidence of an inverse steal in this case in response to the change in arterial PCO_2, it is not possible to say whether reflow in the left parietal cortex was necessarily influenced by intact vasomotor reactivity in collateral vessels.

Regional Differences in rOER within the Ischaemic/Infarcted Region at the Time of the First Study

Study of the OER scan images suggested that the region of elevated rOER at the first study was confined to the superficial area of the early infarct in all cases, although the defect in rCBF and $rCMRO_2$ (and the changes on x-ray CT scan) extended much more medially. This qualitative impression was confirmed on quantitative analysis. Fig. 6 compares rCBF, $rCMRO_2$ and rOER in the ipsilateral and contralateral subcortical grey matter (predominantly lentiform nucleus), and the overlying ipsilateral and contralateral cortex, at the time of the first study in the 6 patients who showed evidence of involvement of the basal ganglia in the infarct. rCBF was depressed to a similar degree in both ipsilateral cortex and lentiform nucleus. However, ipsilateral cortical $CMRO_2$ was preserved relative to that in subcortical grey matter ($2P < 0.025$) and cortical OER was also higher ($2P < 0.05$).

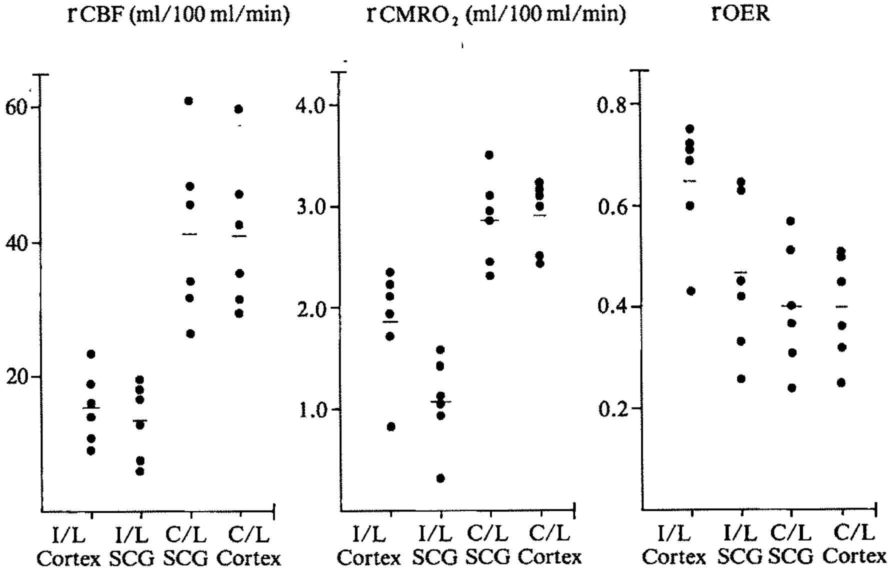


FIG. 6 rCBF, $rCMRO_2$ and rOER in cortex and subcortical grey matter (SCG, predominantly lentiform nucleus), both ipsilateral (I/L) and contralateral (C/L) to the infarct, at the time of the first study on the 6 patients with extensive middle cerebral artery territory infarction. The difference between I/L cortex and SCG for rCBF is not significant, but is significant for $rCMRO_2$ ($P < 0.025$)* and rOER ($P < 0.05$)* * t-test for two-tailed unpaired differences.

TABLE 5. MEAN rOER, IN CORTEX AND SUBCORTICAL WHITE MATTER IN THE REGION OF THE INFARCT, AT THE TIME OF THE FIRST STUDY

	Cortex		*Subcortical white matter*
rOER	0.67 ± 0.13		0.52 ± 0.12
n = 9		$P < 0.025$*	

* t-test for two-tailed unpaired differences.

TABLE 6. MEAN rCBF, IN IPSILATERAL AND MIRROR REGION CONTRALATERAL SUBCORTICAL WHITE MATTER, AT THE TIME OF THE FIRST STUDY

	Ipsilateral		*Contralateral*
rCBF (ml/100 ml/min)	12.4 ± 3.4		22.3 ± 6.4
n = 9		$P < 0.001$*	

* t-test for two-tailed unpaired differences.

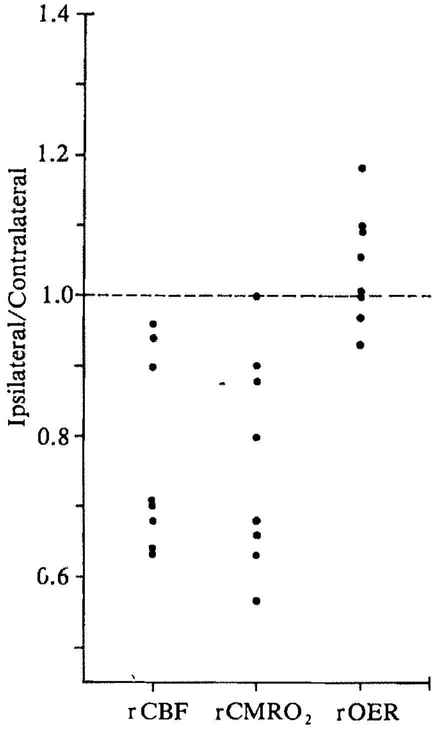
Subcortical white matter similarly showed significantly lower rOER ($2P < 0.025$) than the overlying cortex within the infarcted region at the time of the first study (*see* Table 5). Table 6 shows mean rCBF in the ipsilateral and mirror contralateral region of subcortical white matter, demonstrating that the ipsilateral subcortical white matter had been involved in the ischaemic episode.

Functional Changes in the Region of the Thalami

The x-ray CT scans of all patients showed the thalamus ipsilateral to the infarct to be apparently structurally intact, except possibly in the case of L.B. In all cases the area of hypodensity indicative of infarction abutted against the region of the thalamus. Images on the first PET studies of 8 patients (no plane through the thalamic nuclei was included in the ninth patient) did not show evidence of a significantly elevated rOER in the thalamus ipsilateral to the infarct, compared with the contralateral thalamus. In some cases, however, rCBF and $rCMRO_2$ appeared depressed in a matched fashion. The size of the thalamus created problems when positioning a region of interest 2.6 cm^2 around it on the image, and it was apparent on some studies that an unacceptably large proportion of surrounding white matter was being included within the region. Therefore the one study of a series from each patient that yielded the highest value of $rCMRO_2$ for the thalamus contralateral to the infarct was analysed for values of rCBF and $rCMRO_2$. It was assumed that this plane had been best positioned to display the largest area transaxially of each thalamic nucleus. The ratio ipsilateral thalamus : contralateral thalamus for values of rCBF, $rCMRO_2$ and rOER were then obtained and are shown in fig. 7. The mean time after the onset of stroke of the study from which the values were obtained was 3.5 days ±3 days (range 7 h to 7 days).

In 3 of the patients (J.D., O.T., D.L.), the ratios for rCBF and $rCMRO_2$ were 0.85 : 1.00. As the values for the ipsilateral thalamus were inevitably weighted down by surrounding infarcted white matter, compared with the intact white matter

FIG. 7. Ratio of rCBF, $rCMRO_2$ and rOER in the thalamus ipsilateral to the infarct to the contralateral thalamus. The values for this analysis come from a study within one week of the onset of stroke in 8 cases (the relevant plane was not included in the studies on one patient)—*see text.*



surrounding the contralateral thalamus, the true values for the two thalami were probably equal. The other 5 patients had lower rCBF and $rCMRO_2$ ratios suggesting a functional difference between the two thalamic nuclei despite the x-ray CT scan appearances. Although D.J. and O.T. had the smallest areas of infarction, D.L. had very extensive hypodensity in the territory of the left middle cerebral artery on the CT scan, so that infarct size did not appear to correlate with the functional discrepancy between the two thalami.

Studies on Patient L.B. in Association with Manipulation of Systemic Blood Pressure

Patient L.B. was unusual in that elevation of rOER within the lesion persisted for a much longer period. She was first studied three days after the onset of stroke. It was noted that rCBF in much of the cortex in the ischaemic region was relatively higher than in the other 8 cases at the time of their first studies, and this was also true for $rCMRO_2$ in the ischaemic cortex. The following day rOER had risen in response to a fall in rCBF, without change in $rCMRO_2$. At this time she was relatively hypotensive compared with the recorded blood pressure at outpatient attendances over the previous few years (150/75 compared with 190/95). She was given a low dose angiotensin infusion (0.5 μg/min) to increase systemic blood pressure to her 'normal' level, and improve flow through the dysautoregulated ischaemic region. Fig. 8 depicts CBF, $CMRO_2$ and OER of the left hemisphere cortex before systemic blood pressure had been elevated, and 30 min after it had been increased from 150/75 to 190/95.

rCBF in the ischaemic frontal and temporal cortex rose, rOER fell, but $rCMRO_2$ did not alter. Systemic blood pressure was maintained for a further 24 h by means of the angiotensin infusion. Repeat studies again showed the dependence of flow within the ischaemic zone upon blood pressure. There was no significant improvement in $rCMRO_2$, and no clinical improvement, and the angiotensin infusion was discontinued after 48 h.

Late Studies

Four patients had late follow-up studies (from 17 to 39 days after the onset of symptoms). As it was not possible to do late studies in the other 5 patients, conclusions from the 4 that were performed is limited. In 2 patients there had been little change in either rCBF or $rCMRO_2$ within the infarct compared with the findings at the second study. In the other 2 there was further reflow without a change in $rCMRO_2$, although this reflow in one (L.B.) may have been influenced by the previous angiotensin infusion.

Clinical Correlates with the Observed Pathophysiological Changes

Only 2 patients showed significant clinical improvement over the period of study. Patient G.W. improved between his second and third studies and J.D. between his first and second. Both showed a great increase in power in their hemiparetic limbs but little improvement in their severe dysphasia. No change in $rCMRO_2$

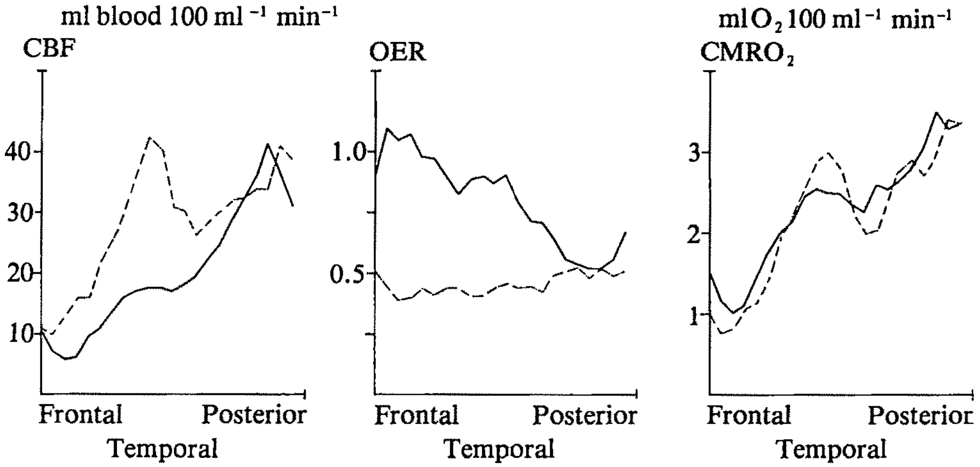


FIG. 8 Cortical CBF, OER and $CMRO_2$ plotted against region of cortex (from anterior to posterior) in patient L.B. before (continuous line), and 30 min after (interrupted line), systemic blood pressure had been elevated. The rOER (and $CMRO_2$) data were not corrected for signal from the cerebral blood volume which accounts for frontal rOER estimated as greater than unity before blood pressure was elevated. (The use of ^{11}CO for rCBV measurement after the first study would have precluded the second ^{15}O study within 30 min, as carbon-11 has a half-life of 20 min). —— = BP 150/75. — — = BP 190/95.

could be detected in the cortex to match this clinical improvement. There remains the possibility that improvement in structures below the resolution of the scanner, such as in the internal capsule, had occurred.

It was apparent that the major pathophysiological changes between the first and second studies were not accompanied by any clinical change in 8 of the 9 patients. Even those patients with a further marked fall in cortical $rCMRO_2$ over this period did not deteriorate clinically. There were, therefore, no features in serial neurological examinations that heralded a change from high to low rOER within the infarcted region.

DISCUSSION

Physiological Findings

Significance of elevated rOER. The fractional extraction of oxygen is normally similar in both grey and white matter. rCBF is regulated to be proportionately in excess of $rCMRO_2$, with the result that the tissues receive a reserve of oxygen supply. This is reflected in the normal rOER of 0.35 to 0.45 (Frackowiak *et al.*, 1980) and $A\text{-}VDO_2$ of 6 to 7 ml/100 ml from a total arterial oxygen content of about 18 to 20 ml/100 ml (Siesjö, 1978). Elevation of rOER will occur during ischaemia to compensate for the reduction in total oxygen supply. The reverse occurs with 'luxury perfusion' observed in association with established cerebral infarcts, when rCBF is disproportionately in excess of reduced $rCMRO_2$. 'Luxury perfusion' can be present with rCBF lower than normal, and measurements of rCBF alone cannot differentiate between ischaemia and 'luxury perfusion' associated with a low rCBF.

Elevation of rOER is only present in the early stages of an infarct on the evidence of this study. This is suggested by the relationship between the age of an infarct and the likelihood of finding a high rOER within the lesion, and confirmed by serial studies on the patients. Mitochondrial function, measured as $rCMRO_2$, persisted in the cortex during early infarction of a large area of middle cerebral artery territory, at a rate that reduced or abolished the normal oxygen reserve in the residual trickle of perfusing arterial blood.

A fall in rOER, indicating supply of oxygen in excess of demand, occurred within the first week in 8 of the 9 cases. This transition resulted variously from reflow, further impairment of mitochondrial function or a combination of the two, and in some instances the reduction in rOER resulted from a fall in $rCMRO_2$ disproportionately greater than a further decrease in rCBF. Whatever the evolution of $rCBF\text{-}rCMRO_2$ relationships in individual cases, the presence of low $rCMRO_2$ and a falling rOER reflected established mitochondrial dysfunction. The follow-up studies between three and five weeks on 4 of the patients showed no evidence of a late rise of $rCMRO_2$, which would have implied delayed mitochondrial recovery.

The obvious practical implication from these observations is that there are many hours after the onset of stroke during which time it may be justifiable to attempt to improve rCBF, or in some other way protect tissue that is potentially only reversibly damaged. After 24 to 48 h it becomes increasingly likely that rCBF will be adequate for residual oxygen demands, and benefit could not be expected to accrue from an increased oxygen supply at this later stage. However, the supposition that an increase of rCBF during the period when rOER is high will 'rescue' neuronal tissue, with clinical benefit to the patient, needs qualification.

It may initially appear surprising that nervous tissue still remains potentially viable, as judged by the use of available oxygen, many hours after the onset of cerebral artery occlusion. Experiments which induced complete cerebral ischaemia in dogs, and were not accompanied by hypotension during the reflow period, suggested that neurological recovery was not possible after about 8 min of ischaemia (Kabat *et al.*, 1941). Then in the early 1960s, revival after 25 min of complete ischaemia in dogs was demonstrated (Neely and Youmans, 1963) and this stimulated research into factors, other than vulnerability of neurons to depletion of energy reserves, that could account for the different experimental findings. One result was the demonstration of the 'no-reflow' phenomenon (Ames *et al.*, 1968), which showed that microcirculatory changes associated with stagnation of blood might limit reperfusion after a period of ischaemia. Subsequently Hossman and his colleagues were able to show return of neuronal function after 60 min of complete ischaemia, under carefully controlled experimental conditions. Although electrical activity (return of the EEG and cortical evoked potentials), synthesis of high energy phosphates and proteins, and recovery of ion and water homeostasis was demonstrated, clinical recovery of the animals (cats and monkeys) could not be assessed because of the experimental conditions (Hossmann and Kleihues, 1973; Zimmermann and Hossmann, 1975; Kleihues *et al.*, 1975). Yet the demonstration that neurons could recover many functions after nearly one hour of total energy depletion suggested a resistance of neurons to ischaemia not previously thought possible. Complete ischaemia results in virtual absence of high energy phosphates after 5 min (*see* Lowry *et al.*, 1964).

The results with complete ischaemia in animals have to be interpreted with caution when extrapolating to regional ischaemia in man. Complete cessation of flow does not occur distal to an occluded cerebral artery unless there is associated profound hypotension, and the partial ischaemia following middle cerebral artery occlusion in squirrel monkeys (Sundt *et al.*, 1969), with complete recovery in some animals after restoration of flow within 2 to 3 h, is a more applicable experimental preparation. It was shown that the fall in ATP and rise in lactate levels in the partially ischaemic region of brain in these monkeys occurred slowly, and there were correlations between the degree of metabolic change and EEG and pathological findings (Sundt and Michenfelder, 1972). Experiments on middle cerebral artery occlusion in baboons has demonstrated that particular neuronal functions decline at sharply defined levels of ischaemia, with loss of ion homeostasis only occurring at a cortical CBF lower than that associated with loss of evoked electrical activity (Branston *et al.*, 1974, 1977). The implication from these animal experiments is clear: partial ischaemia may result in loss of normal neuronal function without inducing the changes that result in irreversible damage for some hours.

Although the demonstration of prolonged viability of partially ischaemic nervous tissue *in vivo* in man is not at variance with results in animal experiments, there is, however, the need for caution in equating elevated rOER with reversible cell damage in the acute stage of stroke. Oxygen uptake *in vitro* has been demonstrated in mitochondria isolated from brain subjected to many minutes of ischaemia, and following which recovery of neuronal function was not demonstrated in other animals subjected to the same length of ischaemia (Schutz *et al.*, 1973). There may also be uncoupling of the electron transport chain from ATP production (Siesjö, 1981). Furthermore, this study has not demonstrated that high rOER in the 9 patients was associated with ischaemia, such that $rCMRO_2$ was only limited by reduced oxygen supply. This phase may have passed by the times of the initial studies, and diminished metabolic demands were already being met by the residual rCBF, albeit by means of increased rOER (a state of diminished perfusion reserve in the presence of partial infarction). This seems to have been the case with patient L.B., who showed no increase in $rCMRO_2$ within the infarcted region in response to an improvement in rCBF. It is relevant to this observation that rOER had increased, secondary to a fall in rCBF, from the day before, but that $rCMRO_2$ had not changed over this period; there had been a diminution of the perfusion reserve over the 24 h between the first and second studies, without rCBF decreasing sufficiently to result in further ischaemia and a fall in $rCMRO_2$. This pathophysiological distinction was then confirmed by the unchanged $CMRO_2$ after the induced increase in rCBF. The use of acute serial studies before and after increase of rCBF will be an effective method of demonstrating reversible ischaemia in future studies, but the means to manipulate rCBF reliably remains to be demonstrated. Increasing blood pressure is only likely to prove effective, and appropriate in the clinical setting, in a proportion of cases.

Even allowing that the values for rOER during the second study on L.B. were not corrected for rCBV, they were probably the highest we observed. On this basis alone the highest rOER values seen in the other 8 patients were below a possible maximum, implying $rCMRO_2$ was no longer limited by oxygen supply at the time of these first studies. The absolute level of rOER might, therefore, help to distinguish ischaemia from diminished perfusion reserve with partial infarction. However, an average rOER of a region which reflects overall only a diminished perfusion reserve might disguise small ischaemic areas with higher rOER. In such circumstances an immediate increase of rCBF might be accompanied by an overall rise of $rCMRO_2$ as the ischaemic areas within the region undergo metabolic recovery.

Significance of OER gradient from cortex to subcortical grey and white matter in the early stage of infarction. As has already been discussed, the pathophysiological criteria of infarction are low $rCMRO_2$ and low rOER. On this basis the presence of a lower $rCMRO_2$ and rOER in subcortical grey matter compared to overlying cortex at the initial studies in the 6 patients with very extensive middle cerebral artery territory damage suggests an earlier onset of infarction in the deeper structures. There is no evidence that neurons in the basal ganglia are more susceptible to ischaemia than those in the cortex, although both regions have subpopulations of neurons that are selectively damaged earlier in ischaemia than others (Siesjö, 1981). The supposition must be that the basal ganglia were subjected to more severe ischaemia than the cortex. The same is probably true of the subcortical white matter, where rOER was also significantly lower than in the overlying cortex at the first study.

The anatomy of the microvasculature (Plets, 1981) may render central tissue prone to more severe ischaemia than the cortex when a leptomeningeal vessel is occluded. There are anastomoses over the surface of the cerebral cortex and the cortex itself is supplied by short perforating vessels, whilst the deeper intracerebral structures, both grey and white matter, are supplied by longer penetrating branches originating from the leptomeningeal vessels. There are also centrifugal branches from subependymal vessels, but anastomoses between these and the centripetal vessels are absent, creating a deep watershed zone. Thus two factors could contribute to greater central ischaemia after reduction of flow in a major leptomeningeal vessel: the absence of collateral flow, and the relatively greater fall in perfusion pressure in the long perforating vessels compared with the short when the pressure in the leptomeningeal artery abruptly declines. A similar mechanism has been used to explain the white matter changes seen in experimental oligaemia in cats (Welsh *et al.*, 1978) and as one of the causative factors underlying the distribution of lesions in hypoxic ischaemic leucoencephalopathy (Ginsberg *et al.*, 1976), which are often present in the basal ganglia as well as white matter.

The results from this series did not show a significant difference in flow between cortex and subcortical grey matter at the first study, despite the difference in $rCMRO_2$ and rOER. This failure to demonstrate a difference in the degree of reduction of rCBF does not refute the previous argument, because even slight inequalities of rCBF in these two regions may have an impact on the length of time mitochondrial function is preserved. The resolution of the scanner would not have permitted a separation of minor, but significant, regional differences in rCBF (*see below*) and, as mentioned previously, animal experiments have shown that loss of particular cellular functions occur at discrete thresholds of reduced rCBF.

Subcortical infarction established early after the onset of stroke will limit any benefit from therapy that might preserve neuronal function in ischaemic cortex.

Ipsilateral thalamic depression. Kuhl *et al.* (1980) reported ipsilateral thalamic depression after middle cerebral artery territory infarction in 5 of their cases studied with fluorine-18-labelled deoxyglucose (to measure regional glucose metabolism) and nitrogen-13 ammonia (a semiquantitative indicator of rCBF) combined with PET. They concluded that the thalamus, predominantly supplied by the posterior circulation, and demonstrated to be structurally intact on x-ray CT scan, was rendered secondarily ischaemic by pressure from surrounding oedema, or had decreased function because of infarction of efferent and afferent connections to the overlying cortex. This series did not demonstrate elevation of rOER that would have been expected, at least during the first few weeks, if ischaemia from raised tissue pressure was present. Although 'disconnection' of the thalamus resulting in reduced metabolism is plausible, it would not explain why one patient (D.L.), with a very extensive area of middle cerebral artery territory infarction, had no asymmetry of rCBF and $rCMRO_2$ between the thalamic nuclei. An alternative explanation might be diffuse infarction of the posterolateral border of the thalamus, not apparent on x-ray CT scan, in those cases which showed asymmetry. This could arise if proximal middle cerebral or internal carotid artery occlusion reduced flow in the anterior choroidal artery, a branch of the first segment of the middle cerebral artery (Plets, 1981). More distal occlusion of the middle cerebral artery, as may have occurred in the 3 patients without thalamic functional asymmetry, would not jeopardize the area of thalamus supplied by the anterior choroidal artery. Further clarification will await the results of PET studies combined with angiography in acute stroke patients.

Technical Considerations

Resolution of the tomograph and reproducibility. The resolution of the scanner compared with the size of the structures in the brain has already been alluded to in the section on data analysis. Values quoted for cortical grey matter will be lower than the true values because of the inclusion of some white matter and subarachnoid space in the 'cortical strip' defined on the numerical printout. Similarly values for white matter will be underestimated where some ventricle has been included in the region of interest used in data analysis, and subcortical grey matter defined on the functional image will include some white matter and/or ventricle. These errors caused by the heterogeneous mix of tissue in a region chosen for analysis, the partial volume effect, has been discussed in detail by Hoffman *et al.* (1979) and Mazziotta *et al.* (1981).

The rOER values give the most useful information for understanding the pathophysiology of ischaemia and infarction. As the OER data are derived from the ratio of the regional radioisotope concentration during $^{15}O_2$ and $C^{15}O_2$ inhalation, the inclusion of a proportion of ventricle or subarachnoid space in a region chosen for analysis has no influence on the true value of rOER; the ratio will not be influenced by the very low radioisotope concentrations in adjacent cerebrospinal fluid.

When investigating the evolution of pathophysiology in a region of brain it is clearly important that the same region is examined with each study of a series. Although a device for very accurate head repositioning in a positron emission tomograph has been described (Bergström *et al.*, 1981), its use requires preparation that would have imposed an unacceptable delay in undertaking the first study on each patient. Therefore small errors of repositioning, inevitable when using an external reference point, were accepted. However, consideration of this problem was incorporated into the presentation of the results. Evolution of rCBF, $rCMRO_2$ and rOER in the cortex have been quoted. The cortical lesions were large and, if repositioning of a patient in the *z* axis of the scanner was several mm in error, only slight discrepancies would be expected by studying the cortex slightly above or below the original line, especially as the slice thickness of the scanner used is 16 mm. The situation is very different when looking at central structures. Grey matter, white matter and ventricle lie one above the other and small errors in repositioning might have a significant impact on the physiological values obtained. Therefore serial values have not been quoted for central structures.

Chronic reproducibility studies on 9 normal volunteers have been carried out in our unit (Frackowiak, 1982). The mean percentage difference between the two studies for values of a region of grey matter in temporal insula was 12 per cent for $rCMRO_2$, 16 per cent for rCBF and 17 per cent for rOER. Although some of this difference undoubtedly reflects physiological variability, it would appear reasonable not to accept mean changes in physiological variables between studies in this series as necessarily significant if less than 20 per cent.

The value of correcting rOER and $rCMRO_2$ for errors arising from signal in the blood pool. The importance of this correction has been fully discussed in the theoretical analysis of the ^{15}O steady-state model by Lammertsma *et al.* (1981). The rOER (and hence $rCMRO_2$) is subject to the greatest overestimation when true rOER is low, rCBV high and rCBF low, a pathophysiological state that might be expected in many infarcts ('luxury perfusion' with low rCBF). The value of applying this correction to the results from the patients in this series, and in other patient studies, has been confirmed in practice (A. A. Lammertsma, personal communication) and this aspect of the use of ^{15}O steady-state model is being prepared for publication.

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NOTICES OF RECENT PUBLICATIONS

Language and Cognition. By Alexander R. Luria. Edited by James V. Wertsch. 1982. Pp. 264. New York and Chichester: John Wiley. Price £17.50.

The late Alexander Luria, who visited this country on a number of occasions in the 50s and 60s, is remembered both for his work in neuropsychology and his remarkable command of the English language. Trained as an experimental psychologist, Luria qualified in medicine comparatively late in life and became very well known for his work on aphasia and kindred disorders resulting from war wounds of the brain. He was a prolific writer, many of whose books were translated into English and widely read in this country. His acquaintance with linguistics, in part acquired from Roman Jackobson, equipped him particularly well to come to terms with the knotty problems of language and its disorders.

The present book is based upon a course of lectures delivered in the University of Moscow not long before Luria's death. Although dealing with much of close interest to neurologists, it is only fair to sound a warning that it is far from an easy book, particularly for those who lack an acquaintance with modern psychology and linguistics. None the less, it provides a clear and instructive account of the development and structure of speech processes and of the principal varieties of speech disorder associated with focal lesions of the brain. As such, it will evidently be of great value to clinical psychologists, speech therapists and others who seek an up-to-date and relatively sophisticated introduction to contemporary neurolinguistics.

Of particular interest to those involved with aphasia are Luria's views on the cerebral localization of speech. While a convinced localizer, he is none the less confident that localization does not exist in the classical form of circumscribed 'centres' whose task it is to generate or comprehend speech. As he sees it, both the comprehension and expression of speech involve a wide range of specialized mechanisms, each of which makes its own specific contribution to language. While there is localization, therefore, it is a localization of component processes rather than a global psychological function.

This line of thinking is well brought out in Luria's discussion of the relations of spoken and written speech. He points out that the structure of written speech differs radically from that of oral monologue or dialogue: spoken speech, he contends, is created in the process of actual social intercourse whereas written speech is from the beginning a conscious and voluntary act in which the means of expression are the main object and focus of attention. One may comment that it is consequently no matter for suprise that writing in organic confusional states is often so grossly disturbed while oral speech remains substantially intact.

Dr J. V. Wertsch, who has translated this book most capably, reminds us in his introduction of Macdonald Critchley's remark that an appropriate summary of the Western investigator's impression of Luria's work can be found in Sydney Smith's statement that '... the further he went West the more convinced he felt that the wise men came from the East'. This may be so, but Luria none the less manages in this book to preserve an admirable balance between Soviet and Western traditions in neuropsychology.

O. L. ZANGWILL

Attention and Schizophrenia. Neurobiological Bases. By Robert D. Oades. 1982. Pp. 343. London: Pitman. Price £22.00.

Few would disagree that if, for all of the psychiatric disorders, we calculated 'comprehensibility ratios'—the number of gathered facts divided by our ability to explain them—then schizophrenia would come top of the list. One reason is the mere complexity of schizophrenia; another is the diversity of levels at which and points of view from which schizophrenic behaviour has been studied. Bravely the author of this book attempts an integration of different kinds of data and theory about schizophrenia—clinical, psychological, neurophysiological and biochemical—his avowed intention being to stimulate interdisciplinary discussion and research. Wisely he eschews any ambition to be all-embracing; instead he confines himself to one feature of schizophrenia, namely, attention dysfunction which, quite rightly in my view, he sees as one of the core features of the disorder and one which, if understood, may help to explain many of its other symptoms.

The book proceeds in a logical fashion, Part I being concerned with the clinical characteristics of schizophrenia and with a review of some evidence about attention dysfunction taken from the experimental psychology and psychophysiology literature. Choice of the latter seems somewhat idiosyncratic; its main purpose seems to be to establish that schizophrenics do have some kind of problem with their attention and to set the scene for Parts II and III, which form the bulk of the book and which look, respectively, at possible neurophysiological and neurochemical bases suggested by the psychological data. Here the author is clearly happier and in both parts he gives us a useful review of evidence that may be relevant for understanding attention dysfunction in schizophrenia. In Part II he considers, in turn, the hippocampus, the basal ganglia, and the prefrontal, posterior parietal and inferotemporal cortices. Part III, in addition to covering the usually quoted evidence on dopamine and 5HT, also examines the possible role of GABA and of the prostaglandins, the steroids and the opioid peptides.

What then does the author conclude? Anyone looking for evidence that schizophrenia is due to a single neurochemical or physiological failure will be disappointed, the 'dopamine hypothesis', for example, being put in what has been evident for some time is its proper place; according to the author's conclusions at the end of each of his systematically arranged sections, any of the brain circuits or chemicals he considers could form the basis of a good theoretical model of attention dysfunction—and probably they are all involved. Oddly Dr Oades does not go on explicitly (though it is difficult to tell because of his rather opaque style) to draw what might be the most logical conclusions: perhaps we will not understand attention *dysfunction* until we understand normal attention, of which the former may only be a special case. This gap in Dr Oades's argument reflects his evidently poorer grasp of the psychological end of his subject matter, which causes him to leave out of consideration attempts that have been made to build interdisciplinary bridges of a different kind—the mapping across to experimental psychopathology of ideas and theories from normal psychology. His own approach is in a more traditional reductionist mould. Despite this criticism his book forms a valuable starting point for anyone trying to find, in a single source, the various neurobiological explanations of schizophrenia currently on offer.

GORDON CLARIDGE

Brain and Intelligence in Vertebrates. By E. M. Macphail. 1982. Pp. 423. Oxford: Oxford University Press. Price £20.00 hardback, £10.95 paperback.

It is one of the central aims of comparative psychology to clarify the mechanisms that underly intelligence. The method is to administer to species of varied intelligence a set of learning tasks and to see what general principles emerge. Dr Macphail's book gives an admirable survey of the data. He starts with two introductory chapters, one on methods of assessing intelligence and one on comparisons of the brain in different vertebrates. There follow five chapters on fish, amphibians, reptiles, birds and mammals. Each reviews the available evidence on the performance of animals in that group on laboratory tasks that test different sorts of learning. Four types of learning are considered, habituation, classical conditioning, instrumental learning and problem solving. The book ends with two further chapters, one on language and intelligence, and one on the conclusions that follow from the survey.

Dr Macphail makes two main claims. The first is that there is no qualitative difference in intelligence between different species of animals although there are differences in degree. He argues that where qualitative differences have been claimed the experiments have not been carried out in equivalent ways on the different animals. The second claim is that people outperform animals because their possession of a language code enables them to cheat, that is, to solve the problems in special ways. The author takes the position that attempts to teach language to apes have not been convincing.

The reader might wonder whether the failure to demonstrate qualitative differences in intelligence between goldfish and monkey may not reflect the poverty of imagination of experimenters in devising suitable tasks. Habituation, classical conditioning and instrumental learning can all be demonstrated in decorticate mammals: indeed classical conditioning is still possible in a spinal cat. It is rather as if IQ was to be measured in people on the basis of the ability to ride a tricycle. Dr Macphail does review the recent claims to teach to chimpanzees the principles of conservation of matter, reasoning by analogy and the understanding of causal relations. He is rightly critical of the tautness of the design of these experiments. But one cannot help feeling that the imagination behind them should be recommended to those who train goldfish.

Readers of this journal will be interested in what is known of the brain mechanisms underlying intelligence. The author gives an up-to-date review of the relevant areas of comparative neurology. However, he contributes more to behavioural theory than he does to neurological theory. He has less to say on why the brain is functionally organized in a hierarchical fashion or whether the mammalian neocortex is a more efficient mechanism for processing information than nonneocortical structures such as the striatal tissue in birds and reptiles.

There is no other recent book that covers the same field. The author has put together a mass of material, and he reviews it with a sound judgement.

R. E. PASSINGHAM

Disorders of Space Exploration and Cognition. By Ennio De Renzi. 1981. Pp. 268. Chichester: John Wiley. Price £16.95.

Neuropsychology books have attempted to be either comprehensive or specialized. The specialized books have usually dealt with language and related disorders. Although some outstanding chapters have been written about spatial disorders, *Disorders of Space Exploration and Cognition* is the first book to be devoted to the subject.

Because Dr DeRenzi and his colleagues have made a large contribution to the understanding of visuospatial disorders, it is appropriate for him to have written this review. It contains nine chapters and covers subjects such as the development of specialization and the relationships of spatial skills, sex and handedness. Disorders of spatial exploration, perception, cognition and memory are also discussed, and there is a chapter dealing with constructional apraxia.

This book is remarkable in that it addresses these topics on four levels—case reports, neuropsychological studies of brain impaired subjects, neuropsychological studies of normal subjects (e.g. using a visual half-field paradigm) and studies of animals (e.g. nonhuman primates). The author successfully integrates this information.

The major weaknesses of this book are that the anatomical substrates for these behaviours are often presented in a quadrantal fashion—that is, right anterior, right posterior, left anterior, left posterior. Dividing the brain into quarters is artificial and does not provide the reader with essential detailed anatomical information. In addition, since Wernicke's work on language disorders, most investigators have treated the brain as a processor rather than a repository. It is unfortunate that processing models have not been developed for the spatial skills discussed in the book. This deficiency reflects the state of neuropsychology as a science rather than the author's skills as writer. However, I had hoped that this synthesis would have induced him to posit new hypotheses.

Despite these deficiencies, the book is an excellent review of what is known. It is recommended as a reference for any neurologist who sees patients with cortical dysfunction and should be read in detail by neurologists, psychiatrists and psychologists who have a primary interest in relationships of brain behaviour.

KENNETH M. HEILMAN

Movement Disorders. Edited by C. David Marsden and Stanley Fahn. 1982. Pp. 379. London: Butterworths. Price £15.00.

Interest in abnormal movement disorders has continued to gather steam since the demonstration more than twenty years ago of a nigrostriatal dopamine deficiency in Parkinson's disease. Unfortunately the intense vocational pressures put upon neuroscientists has led to a plethora of incomplete, brazenly repetitive and unimaginative publications. International symposia have in turn spawned a new arm of the publishing industry dependent for its viability on guaranteed library sales and contributing in no small way to the prevailing literary overkill. However, amongst much that is mediocre and indigestible may be found a number of excellent and easily accessible review articles. For example, first class comprehensive multiple author tomes on the dystonias, Huntington's chorea and Gilles de la Tourette Syndrome are now available. As a consequence, the editors of this, the second in a series of volumes covering particular neurological topics, have had to select their subjects assiduously. They have elected, wisely in my view, to restrict themselves to fields where either a definitive statement can be made or, alternatively, where controversy reigns. The main chapters are, however, supplemented by a series of excellent editorial vignettes.

The first part of the book concerns itself with Parkinson's disease reflecting its importance as one of the commonest physically disabling diseases of old age. After a short introduction by the editors in which current therapeutic dilemmas are aired and the myth of drug holidays dispelled, three incisive didactic chapters on aetiology by Duvoisin, pathology by Forno and neurochemistry by Hornykiewicz follow. The recent work with monozygous twins and HLA tissue typing now suggests that for most patients with idiopathic disease, hereditary factors are relatively unimportant. Rinne's chapter provides an up-to-date account of receptor binding studies in post-mortem material and much of his own recent data is presented. However, this chapter will defeat those not conversant with this increasingly complex field, and I would have preferred to see the more palatable chapters on receptors by Calne and Jenner at the end of the book brought forward. Psychiatric disturbances are now being increasingly studied in Parkinson's disease and Mayeux reviews comprehensively the available literature. The appalling lack of controlled observations in this field make it impossible to decide whether depression and dementia should be considered as integral components of the primary symptom complex. Two chapters by the editors on the phenomenology and pathophysiology of L-DOPA induced oscillations in performance come next. Careful studies of these fluctuations in hospital have shown that the large majority are caused by a progressive reduction in duration of benefit from each L-DOPA dosage, so-called end of dose deterioration, but unpredictable on-off effects or yo-yoing also occur. At least three distinct dyskinetic cycles are also now characterized and hopefully these chapters will encourage clinical trialists to define their terms more precisely. The first half of the book finishes with two chapters on experimental therapies, dopaminergic agonists by Lieberman, and selective monoamine oxidase inhibitors by Stern and Sandler and then a succinct article by Bannister and Oppenheimer on the parkinsonian syndromes associated with autonomic failure.

The next section on myoclonus by Marsden, Hallett and Fahn is probably the most valuable segment of the whole volume. Although the verbose historical review makes somewhat turgid reading and one has to contend with new terms like Baltic myoclonus, the reclassification on pathophysiological grounds is a valuable step forward in attempting to order these confusing disorders. It is a pity, however, that a short section on treatment could not have been included in order to produce a complete overview. The chapter by Mackay on tardive dyskinesias is also worthy of commendation; he states the case for distinct subtypes of the disorder and reviews evidence that temporary discontinuation of neuroleptics may actually promote irreversibility. Shoulson's chapter on the neglected topic of management of Huntington's chorea is also excellent and there then follow a number of short chapters dealing with surgical treatments, the most promising of which would seem to be cervical cord stimulation for athetosis and selective facial nerve avulsion for idiopathic blepharospasm.

This book has been thoughtfully compiled and carefully edited. My only criticisms are of the numerous, irritating grammatical howlers to be found in some of the chapters by the American authors and the rather uneven literary style which inevitably creeps in to multiple author textbooks. One or two of the authors have also allowed their personal prejudices to govern their approach to their subject-matter leading to disproportionate and historically inaccurate reference lists. Overall, I enjoyed reading this book and learnt a good deal. I would strongly recommend it to both neurologists and neuroscientists.

A. J. LEES

Neurofibromatosis (von Recklinghausen Disease): Genetics, Cell Biology and Biochemistry. Advances in Neurology, Volume 29. Edited by V. M. Riccardi and J. J. Mulvihill, 1981. Pp. 282. New York: Raven Press. Price not stated.

This volume arose as the result of a recommendation made by a workshop on Biologic Approaches to Neurofibromatosis. As such it is a hybrid, much better than most conference proceedings but perhaps not as comprehensive as most multiauthored monographs. The clinical aspects of neurofibromatosis occupy only about one-quarter of the book. Emphasis is given to new observations, of which those concerning associated malignancy and the 'central form' of the disease (bilateral acoustic neuromas with little cutaneous involvement) are particularly interesting.

Approximately two-thirds of the text concerns the biology of neural crest tissue and nerve and other growth factors. Application of some of the studies to the clinical problem is not always immediately obvious.

One of the final chapters should be helpful for the clinician in that it summarizes the difficulties in defining criteria for the diagnosis of neurofibromatosis, especially in borderline cases. The often unsought Lisch nodule is rightly stressed as being important in this context. The last section includes a brief biography of von Recklinghausen and a translation of his original case reports together with some of the figures.

This book should be of interest to neurologists, geneticists and neurobiologists. It emphasizes how much is unknown about a disease which affects 1 in 3000 or more of the population.

A. E. HARDING

Handbook of Clinical Neurology. Volume 43. **Neurogenetic Directory** Part II. Edited by N. C. Myrianthopoulos, P. J. Vinken and G. W. Bruyn. 1982. Pp. 636. Amsterdam: North Holland Publishing Company. Price not stated.

The second part of the *Neurogenetic Directory* is the 43rd and last volume of the *Handbook of Clinical Neurology*. It appears just thirteen years after the first. The editors must either be heaving huge sighs of relief or planning a second edition.

This volume is a continuation of the first part of the Directory, with multiple authors contributing to sections on neurocutaneous syndromes, autonomic dysfunction, muscle disease, psychiatric disorders and mental retardation. Syndromes comprising congenital abnormalities, including chromosomal aberrations, associated with neurological problems are also described. Coverage is comprehensive and not as uneven in terms of quality as might be expected from the number of contributors. The index to both neurogenetic volumes is adequate but it does allow the unwary to encounter the same disease under different labels. Although the classification of neurogenetic disorders is fraught with difficulties, some guidelines from the editors would have been very helpful in this instance.

A. E. HARDING

Surgical Pathology of the Nervous System and its Coverings. By P. C. Burger and F. S. Vogel. 2nd Edition. 1982. Pp. 739. Chichester: John Wiley. Price £50.50.

This attractive volume presents the material derived from the intake of a busy neuropathology department with apparently very good photographic facilities. Topics covered include any condition which might be encountered in a neurosurgical biopsy, with the expected emphasis on tumours, but illustrative specimens derived from autopsy are also used. This is not a reference book, it is not comprehensive and does not treat any subject in depth but rather ranges over the nervous system, its bony and fibrous coverings and peripheral nerves, illustrating the pathological conditions which the authors have encountered but omitting those which probably they have not encountered. The illustrations are the oustanding feature of the book. The high quality of macroscopic and light and electron microscopic photographs is consistent throughout and their importance is emphasized by the inclusion of an illustration index. References accompanying each section suggest that the reader should look elsewhere for information to supplement the photographs. The intention of the authors seems not to instruct but to share their experience and it is a pleasure to do so, albeit an expensive one.

L. W. DUCHEN

Intervention Radiology. 2. International Congress Series 575. Edited by L. Oliva and J. A. Veiga-Peres. 1982. Pp. 344. Amsterdam: Excerpta Medica. Price Dfl. 160.00.

This volume is mainly in the field of general angiographers and interventional radiologists but it does contain a few papers of neurological interest. One of these concerns the successful treatment by transluminal angiography of a long segment of fibromuscular dysplasia associated with hemiplegia in a young woman. Another detailed case report is of a child suffering from 'blue rubber bleb nevus syndrome' with a posterior fossa haemangioma supplied exclusively by one occipital artery and which regressed after gelfoam embolization. Papers on percutaneous destruction of the gasserian ganglion using the method described originally by Sweet and on percutaneous cordotomy include discussion of indications, technique and results and provide good reviews of the subject related to personal experience. Many neuroradiologists will be interested in experimental results with new tissue adhesives, silicones and alcohol and in papers discussing embolization of intraosseous haemangiomas of the mandible and of aneurysmal bone cysts.

The book should be available in neurological libraries for reference to the articles mentioned, but it is unlikely that neuroscientists will personally wish to purchase the volume.

BRIAN KENDALL

Current Topics in Neurobiology: Neuroimmunology. Edited by J. P. Brockes. 1982. Pp. 256. New York and London: Plenum Press. Price $29.50.

Anyone expecting this symposium to review the immunology of the nervous system and its diseases will be disappointed. Instead, it concentrates on the application of immunological methods in neurobiology, especially in defining markers specific for cell types in the CNS and in the neuromuscular field. Most of the essays concentrate on the contributions of the authors' own groups, often with rather sparse cross-reference to others. That has the advantages that the essays are up to date and well illustrated. However, the reader who wants to cross-link findings between groups often finds himself left on his own (though helped by a good index).

As most of the articles show, we are still in the twilight phase between the occasionally murky work employing conventional antisera and the dawning of the monoclonal era. As yet, it has mainly spotlighted the most obvious landmarks, for example, by providing antibodies specific to astrocytes, oligodendrocytes or Schwann cells, or to neurons of the CNS or PNS as a whole, though there is already the usual crop of unexpected 'cross-reactions'. The development of antibodies to crucial functional molecules such as receptors for transmitters, ion channels and, above all, specific cell recognition structures, is apparently only just beginning. The high noon in this field will come when these antibodies can be used to study and manipulate developmental interactions, or possibly neuronal membrane physiology: from this symposium, that exciting time would seem to be a few years away yet.

Perhaps the core of this collection, then, is in the last three articles. An excellent one from C. J. Barnstable describes three monoclonal antibodies (Mc ab) that label membrane components of distinct segments of retinal rods, but no other cells in the retina—the only example in the book of antibodies specific to a *subset* of neuronal cells. As with the next two essays, ontogenetic studies have revealed differences between the antigens detected even before they have been characterized biochemically. So too with Barnstable's six Mc ab against Müller cells—specialized radial astroglial cells of the retina. He also discusses strategies for raising and screening Mc ab to key functional molecules: it is a tantalizing thought that some of these may already have been raised and missed

R. Mirsky and M. Schachner each review about seven years' work from their respective laboratories on cell markers in the CNS and PNS. Progress has been most rapid with glial cells, and one interesting finding concerns the specialized subset of radial astroglia which include Müller cells and the Bergmann glia of the cerebellum. In addition to their embryological affinities, these prove to share some distinctive antigens (such as Schachner's C_1). The Bergmann glia apparently act as guideposts for the migration of the granule cells during cerebellar development, and there are faint hints implicating C_1 antigen in this process. Barnstable suggests that the Müller cells may play a similar role in the retina.

Surprisingly, both these cell types also share antigens with ependymal cells—which suggests that some ontogenetic trees may eventually need to be redrawn. That will require several independent markers, however; there are already enough examples of 'cross-reactions' or 'convergent ontogeny' to show that any one marker used in isolation may be misleading. For example, the 'glial' cells in the enteric plexus are derived from neural crest, and express one Schwann cell marker (Ran-1), but yet contain filaments normally characteristic of astrocytes.

For the cell biologist there is also much discussion of the cell types producing fibronectin and vimentin, among other markers. Some of these can now be used to identify (and sometimes purify) astrocyte, oligodendrocyte and Schwann cell precursors, and to study the ontogeny and physiology of several cell types *in vitro* and *in vivo*. In a few more years, there will surely be exponential progress from this starting-point.

Only one essay is a truly comprehensive *review*—that by R. B. Kelly and Z. W. Hall on the antigens of the neuromuscular junction. Here there is an excellent and very up-to-date discussion of components of the synaptic cleft as well as of pre- and postsynaptic regions, with very little bias towards the authors' own work. They give a valuable introduction, and stick rather strictly to their immunological brief, with only passing reference to work with biological toxins (probably for brevity). Their very extensive consideration of the nicotinic acetylcholine receptor (AChR) and its Mc ab is a fair reflection of the outstanding recent progress in that area.

Also in the neuromuscular field, D. M. Fambrough *et al.* exploit one Mc ab to purify myotubes. They then show that these synthesize fibronectin in culture with kinetics very similar to those they have previously found for both AChR and ACh esterase—perhaps implying some common 'packaging' process. Another Mc ab recognizes an antigen that often coincides in distribution with AChR, but is in the basal lamina—which is known to be important in neuromuscular junction formation. A third

Mc ab against myoblasts and satellite cells unexpectedly binds to Schwann cells too—perhaps another example of 'convergent ontogeny'.

W. D. Matthew *et al.* have raised a battery of Mc ab to rat brain synaptosome preparations, many of which recognize neurons or oligodendrocytes: only a minority are specific for synapses and some of these for only a minority of synapses. These reveal an unexpected heterogeneity in the synaptosome preparation; only about 20 per cent of the 'synaptosomes' bear one antigen characteristic of synaptic vesicles. Remarkably, the relevant Mc ab (somewhat misleadingly called 'serum 30') apparently binds to almost all synaptic vesicles regardless of product or site, in shark, frog and chicken as well as mammalian species. It is also found in all the neurosecretory cells tested.

Finally, there is a short and thoughtful essay by L. L. Y. Chun and H. Cantor on some of the lessons to be learnt from the study of markers for T lymphocyte subsets that could be relevant to neurobiologists.

In conclusion, this symposium provides an interesting summary of much of the existing groundwork on cell markers in neurobiology. Most of the articles are quite readable and will surely be helpful to both the specialist and the very interested outsider.

H. N. A. WILLCOX

Cortical Sensory Organisation. Volume 1. **Multiple Somatic Areas.** Edited by Clinton N. Woolsey. 1981. Pp. 272. Clifton, New Jersey: Humana Press. Price $44.50.

In general I am not enthusiastic about the published proceedings of symposia, for they rarely contain material that has not been previously published elsewhere. However, this volume, which is one of three covering the field of the brain's sensory organization, is a notable exception because it is a wide-ranging and detailed account of the present state of knowledge about the multiple fields in the somatosensory cortex. It is the proceedings of a symposium, held in Dallas in 1979, on multiple somatic, sensory motor, visual and auditory areas and consists of eight separate contributions.

In the early 1940s, it was thought that the cortical representation of somatic and visual inputs had a single topographical location. Since that time it has become increasingly obvious that there are many cortical areas related to these systems; for example, it is now thought that at least a dozen cortical areas of representation of visual inputs exist. Those concerned with somatosensory inputs are of course less numerous, but with the advent of modern recording methods we may expect the number of recognized areas also to increase.

This book gives detailed and up-to-date information on the somatosensory areas (volumes 2 and 3 deal with multiple visual areas and multiple auditory areas, respectively) beginning with a discussion of Sm I in prosimian primates, the postcentral somatosensory cortex and SI cortex. The organization of SII parietal cortex and somatic cortex are then described and the concluding chapter deals with intracortical connections.

The editor is Clinton Woolsey, the pioneer in this field, and he has persuaded a team of neuroscientists who are in the forefront of research to contribute. The book is an invaluable work of reference for everyone who is interested in the anatomy and physiology of the brain, particularly in the specific and multiple representations that the somatic areas have within the cerebral cortex.

O. C. J. LIPPOLD

Neurotransmitters, Seizures and Epilepsy. Edited by P. L. Morselli, K. G. Lloyd, W. Loscher, B. Meldrum and E. H. Reynolds. 1982. Pp. 378. New York: Raven Press. Price $57.12.

This is a collection of 30 papers presented at a workshop on the involvement of putative amino acid transmitters, mainly GABA, in brain seizures. Mention nowadays a new proceedings of a symposium in scientific circles and two diametrically opposed views will be forthcoming *viz.* (*a*) a useless reiteration of summaries of published work *versus* a convenient source of present ideas on a subject and (*E*), a meeting of the 'in-crowd' getting together to pat their own backs once again with the noninvolvement of the younger developing worker with new ideas *versus* a meeting of a well-chosen group of specialists who actually know what they are about. Such unreasonable blackness and whiteness, of course, never exists in reality. Symposia are where the good, bad or just indifferent present their papers well, badly or indifferently. This present tome is a fairly typical example.

Almost all the papers start by pointing out the literature of the possible involvement of their chosen amino acid in epileptic activity and conclude that their present work leads to the suspicion that their chosen amino acid is indeed involved in epileptic activity. The papers range from an example of the classic jocular definition of a drug 'anything which injected into an animal produces a paper', *via* one which eulogizes the drug produced by the firm which provided financial support for the symposium to a paper which makes really fascinating reading for the ratio of assumptions to not yet knowns. One of the key papers, in my view, which pointed out that for definitive attacks on the pharmacology of amino acid transmitters much more potent and specific agonists and antagonists were required seems, judging from the discussion, not to have achieved sufficient impact.

There are some very good papers in this book, mainly those that look at the compartments from which the amino acid concentrations are measured, the properties of the amino acid receptor-ionophore complex, the behaviour of inhibitory systems under prolonged activation, the interaction of various transmitter systems, the effects of putative transmitters on cerebral haemodynamics, the examination of transmitter metabolites in patients and the anatomical distribution of GAD-containing nerve terminals at electrically hyperactive foci.

The book poses many more questions than it answers and a lot of the discussions to the papers produce confusion rather than clarity.

A. ANGEL

Sensorineural Hearing Loss, Vertigo and Tinnitus. By M. M. Paparella and W. L. Meyerhoff. Ear Clinics International, Volume 1. 1981. Pp. 181. Baltimore and London: Williams and Wilkins. Price $31.00.

This publication is the first of what is intended to be an annual production on topics of otological interest discussed at the Ear Clinics International meetings. The editors aim to produce a series of didactic chapters rather than a slavish report of the proceedings of the meeting. Since these volumes are primarily intended for the otologist and practitioners of allied disciplines it is not surprising that the first publication is of limited interest to the neurologist and neurosurgeon.

The book is divided into sections dealing with current trends in audiology, sensorineural hearing loss, hearing aids, tinnitus and vestibular problems. As with all multi-author volumes there is a patchiness of style, content and value. The chapters by Hallowell Davis are as usual succinct and have a clarity not found in all the other sections. The section on vestibular testing by Barber will be of interest to the neurologist and it is refreshing to see a considerable portion of the chapter devoted to caloric testing, so often eschewed by otologists. Liden and Rosenhall's account of new developments in diagnostic audiology is a useful introduction to some of the perversions of auditory function found in patients with neurological disorders, disturbances not widely appreciated by the practising neurologist, for example, abnormalities of directional hearing. Other chapters such as those on cochlear implants are of general interest. Most of this book, however, is of little interest to neurologists. This is no doubt partly because it is intended for other specialists and also unfortunately because some of the chapters are poorly written, impart little information and even on occasion, have no references.

PETER RUDGE

NEUROANATOMY AND NEUROSCIENCE

Principles of Neuroanatomy. By Jay B. Angevine, Jr. and Carl W. Cotman. 1981. Pp. 393. Oxford and New York: Oxford University Press. Price £8.95.

Evolution of the Nervous System. Second Edition. By Harvey B. Sarnat and Martin G. Netsky. 1981. Pp. 504. Oxford and New York: Oxford University Press. Price £9.95.

Principles of Neural Science. By Eric R. Kandel and James H. Schwarz. 1981. Pp. 731. London: Edward Arnold. Price £22.50 paper, £45.00 boards.

The Nervous System. Second Edition. By Peter Nathan. 1982. Pp. 298. Oxford: Oxford University Press. Price £12.50.

The development of neuroscience or neurobiology as a separate discipline has, at least temporarily, led to a blurring of the traditional distinctions between neuroanatomy, neurophysiology, neuropharmacology and neurochemistry. This is illustrated, to a greater or lesser degree, in the four books reviewed here.

Principles of Neuroanatomy by Angevine and Cotman is predominantly on the structure of the human nervous system. Nevertheless, it is written jointly by a neuroanatomist and a biochemist and embodies a substantial section on the chemical coding of neural circuits. It also differs from most of the previous texts on the anatomy of the nervous system by emphasizing the general principles of the organization of the brain, spinal cord and peripheral nervous system. The brain, in particular, is difficult to comprehend sensibly unless it is understood in terms of its ontogenetic and phylogenetic development. Unfortunately the embryology is dealt with in somewhat too cursory a manner, and evolutionary aspects are mentioned only in passing. Nevertheless, the book provides a much more comprehensible account of the nervous system than most others that are available and relates structure to current views as to functional organization in an interesting and helpful manner. References are also made to disordered function, although the neurological comments are at times a little naïve. Thus sparing of the ability to write is given as a particular feature in parkinsonism. An opportunity is also missed in relation to cerebellar disorders which are dealt with rather briefly and incompletely. The book is mainly directed towards undergraduate students but, although concise, is sufficiently comprehensive to be of interest to clinical neurologists. It has an attractive direct style and is excellently illustrated, mainly by line drawings.

The second edition of *Evolution of the Nervous System* by Sarnat and Netsky complements the above work. The first edition established itself as an authoritative account of the comparative anatomy of the vertebrate nervous system with an attempt to derive from this the probable evolutionary sequence of events. The second edition has been extensively revised and incorporates new chapters on the comparative neurochemistry of the vertebrate nervous system, on the development of neuromuscular control and on the evolution of cerebral structures in relation to behaviour. Teleology abounds in the last, but these are welcome additions which should enhance the value of this interesting and highly readable book.

Principles of Neural Science, edited by Kandel and Schwarz, clearly emphasizes the spirit of neuroscience as a unitary discipline. It is dedicated to Stephen Kuffler who played such an important role in bringing cohesion to the subject. The book is designed as an introductory text for students of biology, behavioural science and medicine and gives as its aim the intention of conveying 'the interest and excitement surrounding the recent attempts to apply cell-biological techniques to the study of the nervous system, its development, and its control of behaviour'. It is written by 20 members of the staff of the College of Physicians and Surgeons of Columbia University, New York, and ranges widely over the cell biology, morphology and physiology of the nervous system, and their relevance to behavioural science, clinical neurology and psychiatry. It undoubtedly succeeds in providing a fascinating introduction to the organization of the nervous system, with a strongly clinical slant, and is clearly written and presented. The practice of a number of the contributors of using synoptic statements as section headings, although sometimes helpful and arresting, is at others rather banal and irritating.

The Nervous System by Peter Nathan has the same general aim as the previous book, namely, to provide an introduction to current knowledge as to the organization and function of the nervous system, but it is aimed at the informed layman. Although based on his previous Pelican book, with the same title, it has been extensively revised. Peter Nathan writes with an engaging, laconic, personal style and, for those who know him, it is easy to hear him speak the words as one reads the book. It is punctuated by flashes of his characteristic wit. 'Sleep and pain', he writes, 'tend to inspire poets and philosophers; micturition and defaecation do not. With psychoanalysts, it is the other way round.' The arguments are supported by numerous illustrations taken from the whole of the animal kingdom and from clinical neurology, ranging from echolocation in bats to the experiences of astronauts in space. This delightful short book can be recommended to the novice and sophisticate alike.

P. K. THOMAS

Pituitary Hormones and Related Peptides. Serono Symposia, Volume 49. Edited by M. Motta, M. Zanisi and F. Piva. 1982. Pp. 406. London: Academic Press. Price £32.00.

Neuroendocrinology has advanced at an incredibly rapid rate since the influence of the central nervous system on endocrine function and the effects of hormones on the brain first became evident. An enormous number of papers, review articles and books on the subject has been published. *Pituitary Hormones and Related Peptides* is a record of the proceedings of the 49th Serono Symposium. It deals comprehensively with the chemistry and control of secretion of anterior and posterior pituitary hormones. Among recent developments, the role of neurotransmitter substances in controlling the secretion of hypothalamic releasing hormones is considered in detail, as also are newer aspects concerning the regulatory effects of the target organ hormones on the functional activity of the pituitary gland. Attention is given to the biochemistry of the opioid peptides, including their relationship to corticotrophin, and to their possible use in the treatment of certain psychoses, but their role in the control of endocrine activity is hardly mentioned. The book also contains a few unrelated chapters of clinical interest.

The first chapter is packed with information stated clearly and concisely and it provides an admirable introduction to neuroendocrinology. The following chapters which suffer from differences in style and presentation because of the large number of contributors, are devoted to topics which appear to have been chosen capriciously. Some authors have reviewed their specialized topics and included their own work in its proper perspective but others have used the book as an opportunity to gather together, sometimes indiscriminately, previously published data and publish it yet again. Many of the contributions illustrate clearly how the development of radioimmunoassay techniques has accelerated the accumulation of data and led to the publication of a plethora of papers of debatable scientific value. Others show how the confusion has been exaggerated by the indiscriminate use of biological methods by workers who appear to be unfamiliar with the fundamental principles of biological standardization. Despite its limitations the book answers many questions and poses many more. It will be invaluable to workers embarking on research in neuroendocrinology and to others attempting to keep up to date in a very rapidly expanding field.

J. R. HODGES

ANNOUNCEMENTS

Establishment of an International Register of Familial Brain Tumours

An International Register of Familial Brain Tumours (IRFBT) has been established at the Comprehensive Cancer Centre, Leyden, The Netherlands, following the publication of an initial register (Tijssen *et al.*, 1982). The IRFBT is engaged in the active search for new cases of familial brain tumours and would like to invite clinicians worldwide to submit cases, either published or unpublished, to this register. Care will be taken to update the register at appropriate times.

TIJSSEN C C, HALPRIN M R, ENDTZ L J (1982) *Familial Brain Tumours, a Commented Register.* The Hague: Martinus Hijhoff.

Address: IRFBT, Comprehensive Cancer Centre, Vondellaan 47, 2332 AA Leyden, The Netherlands.

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The Fyssen Foundation's general aim is 'to encourage all forms of scientific enquiry into cognitive mechanisms, including thought and reasoning, underlying animal and human behaviour, into their biological and cultural bases, and into their phylogenetic and ontogenetic development'.

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The nominations should include a curriculum vitae of the nominee, a list of his publications and a summary (four pages maximum) of the research work upon which the nomination is based.

Nominations for the 1983 Prize of the Fyssen Foundation should be sent (*15 copies*) to the Secretariat of the Foundation, 194, rue de Rivoli, 75001 Paris, *before September 1, 1983.*

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July 11–15, 1983

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Guest faculty will include: Professor W. F. Hoyt, San Francisco, Professor H. S. Thompson, Iowa, Dr Lars Frisén, Sweden, Dr M. Behrens, New York, Dr U. Büttner, Dusseldorf.

For further information please apply:

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Department of Neuro-ophthalmology,
The National Hospital for Nervous Diseases,
Queen Square, London WC1N 3BG
Tel.: 01-837 3611 Ext. 221 or 222

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'The author has maintained a balance between clinical and scientific content which will ensure the continued importance of the book to all who require information about the human nervous system.' *The Lancet.*

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1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:
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   (b) Statement of age and post currently held;
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Critical perfusion of brain and retina. R. W. Ross Russell and N. G. R. Page 419

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Notices of recent publications 525

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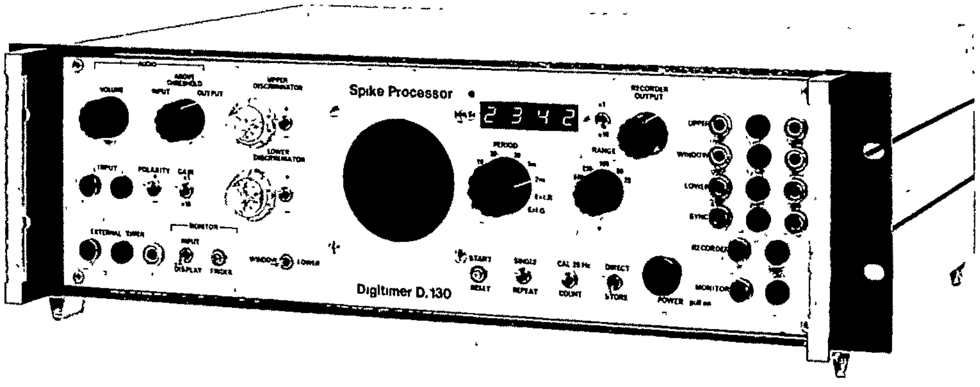

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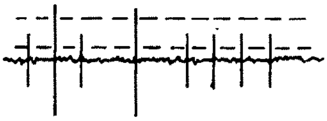

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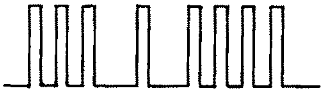

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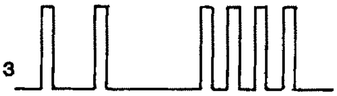

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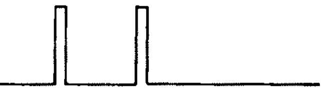

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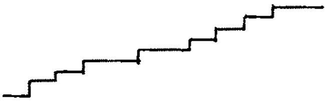

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Norman C. Nevin and Josephine A. C. Weatherall

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'UTILIZATION BEHAVIOUR' AND ITS RELATION TO LESIONS OF THE FRONTAL LOBES

by F. LHERMITTE

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SUMMARY

A new type of behaviour, termed 'utilization behaviour', was observed among patients affected with left or right unilateral, or bilateral, frontal lesions. It is an extension of bilateral manual grasping behaviour (magnetic apraxia). The tactile, visuotactile and visual presentation of objects compels the patients to grasp and use them. This behaviour was obtained with miscellaneous utilitarian objects. For the patients, the presentation of objects implies the order to grasp and use them. It is proposed that the balance between the subject's dependence on and independence from the outside world is disturbed. With frontal lesions, the inhibitory function of the frontal lobes on the parietal lobes is suppressed. The result is a release of the activities of the parietal lobes so that the subject becomes dependent on visual and tactile stimulation from the outside world. Five cases are reported as examples: one anatomoclinical case with bilateral lesions of the frontal lobes, one case with lesions in the left frontal lobe and three cases with lesions in the right frontal lobe. The role of lesions affecting different parts of the frontal lobes is discussed. The neuropathological observations lead to the suggestion that lesions of the orbital surface of the frontal lobe, and perhaps of the head of the caudate nucleus, are responsible for this behaviour.

INTRODUCTION

Wilson and Walshe (1914) had already observed the grasping reflex before Adie and Critchley (1927) described 'forced grasping' and 'groping' in relation to lesions of the contralateral frontal lobe. Denny-Brown (1956, 1958) used the term 'magnetic apraxia' for more elaborate manual activity in which the patient tries to grasp objects presented by the examiner as tactile and visual stimuli. In most instances, this activity is *unilateral.* Denny-Brown (1958) interpreted this as a release of parietal lobe activity following suppression of inhibition by the frontal lobe. Other authors have also observed it after unilateral lesions (Castaigne *et al.*, 1961) or bilateral frontal and diffuse lesions of the cerebral cortex (Tissot *et al.*, 1975).

In this paper, the proposal is made that *bilateral* magnetic apraxia corresponds to the release of parietal psychomotor behaviour, but at a higher level than suggested by Denny-Brown (1958). The expression 'manual grasping behaviour' seems more appropriate. Our purpose is chiefly to describe and interpret a new aspect of the behaviour resulting from lesions of one or both frontal lobes: the presentation of everyday objects within reach of the hands or in the field of vision impels the patient to grasp and use them. We suggest calling this 'utilization behaviour'.

PATIENTS

Initially, in 1968, whenever utilization behaviour was observed, the same behaviour was examined in a normal subject and in another patient suffering from a cerebral lesion that did not affect the frontal lobes. This study has since been performed in more than 100 normal subjects and in a considerably greater number of patients. The evaluation became routine during clinical examination of all patients with cerebral lesions. The details of the examination procedure are discussed later under Methods and Results.

We at first began classifying cases of utilization behaviour due to bilateral frontal lesions. As the years elapsed, we observed this behaviour so frequently in cases when (but only when) there was bilateral manual grasping behaviour (magnetic apraxia) that documentation of bilateral frontal lesions was discontinued. From 1968 until March 1982, more than 40 cases of utilization behaviour with bilateral lesions of the frontal lobes were observed (Alzheimer's disease, frontal glioma considered to show bilateral involvement, surgically treated aneurysms of the anterior communicating artery). In Alzheimer's disease, we have only taken into account patients in whom neuropsychological examination revealed the existence of frontal signs (apathy, nonfluent aphasia, disturbances in the sequencing of gestures, pseudoamnesia and sphincter disorder), with no signs of right or left parietotemporal affection (such as ideomotor and ideational apraxia, amnestic or conduction aphasia, left-sided spatial neglect). In this article we describe the case of a female patient with bilateral frontal lesions, chosen because a neuropathological study was undertaken, and 4 cases of unilateral frontal lobe lesion (one left-sided, 3 right-sided).

CASE HISTORIES

Case 1 (No. 36.675)

A right-handed social welfare inspector, was aged 62 years when she developed, on January 4, 1975, a subarachnoid haemorrhage with sudden headache and loss of consciousness for about 10 min, followed by disorientation and incontinence. The CSF was haemorrhagic and angiography revealed a large aneurysm connected by a small neck to the second segment of the right anterior cerebral artery or the anterior communicating artery. The only previous history was of a sudden episode of loss of consciousness for 20 min, without convulsions but with urinary incontinence nine years before. The patient was operated upon on January 29, 1975 (Professor Pertuiset). Since the rupture made ablation of the aneurysm impossible, a Yasargil clip was applied to the neck. The right frontal lobe was obviously damaged over an area of roughly 2 cm^2. Post-operative recovery was uneventful, apart from a severe frontal syndrome which continued to worsen (somnolence and incoherent speech, together with urinary and faecal incontinence), because of which a ventricular CSF shunt was inserted on March 14, 1975.

One month later, neurological examination revealed difficulty in maintaining upright posture because of retropulsion. Muscular power was normal. The tendon reflexes of the upper limbs were brisk. The plantar responses were flexor. Vision and sensation were normal. The sphincter difficulties had subsided. The remainder of the examination was normal. Language was not aphasic and gestures were normally performed. Conversation was unimpaired and psycholinguistic achievement was normal. Reproduction of a story was normal; narration of 'Little Red Riding Hood' was also normal, apart from some perseveration. Luria gestures and drawings were correctly executed, with few perseverations. Memory for past and recent events was normal; the patient gave precise information as to her surgical operations. She remembered correctly stories that she had been told several minutes before. She knew she was in the Salpêtrière Hospital. However, she was unable to remember the dates of the days when she was examined. She made mistakes in mental calculations.

Bilateral manual grasping behaviour was obvious. Utilization behaviour was obtained for a glass and a jug of water, an apple and a knife, a banana, bread, a nail, a plane and a hammer. Moreover, when she took hold of a plate, a knife and a fork, she imitated the gestures of cutting the food and bringing it to her mouth. This behaviour rapidly declined and then ceased. One month later, the frontal syndrome had completely disappeared. Memory was considered as 'excellent', but mentally she was somewhat slow. Later, the patient wished to return to work. She had two epileptic attacks, but these have not recurred since treatment with phenobarbitone.

An EEG (May 5, 1975) revealed prominent slow waves in bilateral anterior corticosubcortical areas, predominantly on the right side. An isotope gamma scan showed the existence of a right corticosubcortical anterior frontal lesion, 3 cm long and 2 cm deep. General examination was normal, with the exception of a variable elevation of blood pressure.

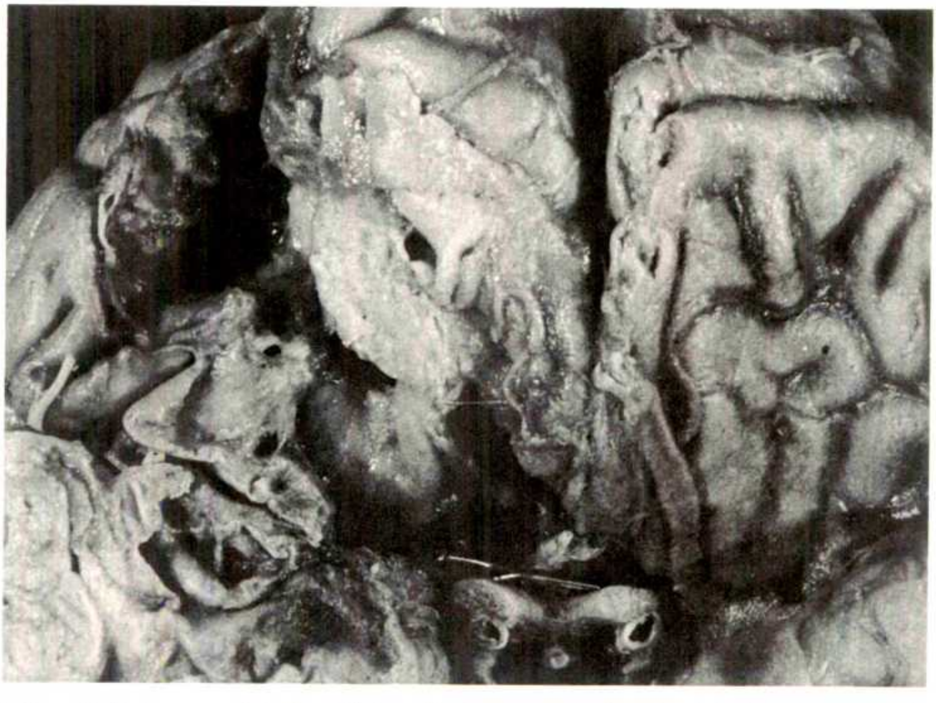

FIG. 1. *Case 1.* Inferior aspect of the frontal lobes with the neurosurgical scar involving lateral cortex of the right frontal lobe.

This patient was not observed in the course of the ensuing months. We were informed that in the Spring of 1976, she had several ischaemic vascular episodes involving the right and left hemispheres. She was admitted to the neurosurgery department (Professor Pertuiset) where she died because of a deterioration in her general state and bronchopneumonia. The postmortem examination was performed by Dr F. Gray (Charles Foix Laboratory).

Macroscopic examination of the brain (1100 g). A cavity related to the surgical operation was found in the right orbital lobe (fig. 1). Old ischaemic lesions had destroyed the head of the caudate nucleus on both sides and extended on the left to the entire territory of Heubner's artery. The corpus callosum showed a haemorrhagic lesion in its midportion and was seriously atrophic anteriorly. Several recent infarcts were observed in the territories of the right and left middle cerebral arteries and in the left posterior cerebral artery. A clip was found on the neck of the aneurysm in the anterior communicating artery. No aneurysm remained. The initial segments of the anterior cerebral arteries were shrunken but unobstructed; the right pericallosal artery was atrophic and occluded.

Microscopic examination of the brain. The operation site appeared as a necrotic cavity affecting both orbital lobes, but larger on the right (fig. 2A). Numerous old ischaemic lesions, certainly present at the time of operation, were observed (figs. 2B and C) in the territory of Heubner's artery on both sides and in the deep and anterior territory of the left middle cerebral artery. The corpus callosum showed numerous necrotic foci, in particular in its anterior part which was atrophic. The white matter of the anterior part of the centrum ovale of the two frontal lobes showed diffuse demyelination, sparing the U fibres (fig. 2A). The latter was related to the necrotic lesion of the corpus callosum, hydrocephalus and numerous foci of lacunar necrosis. *Recent* ischaemic lesions were observed in the territories of both middle and the left posterior cerebral arteries. The mamillary bodies, both Ammon horns, the thalamus and the posterior part of the cingulum were normal. There were diffuse vascular lesions, with hyaline arterial degeneration and dilatation of the perivascular spaces together with macrophages that often contained haemosiderin.

Case 2 (No. 30.785)

A right-handed male Post Office worker, aged 35 years, had a generalized epileptic seizure on October 11, 1973 without premonitory phenomena and without any postictal deficits. The patient had no previous history of neurological disease and was asymptomatic. Neurological examination was normal. An EEG (October 12, 1973) revealed intermittent paroxysmal slow activity, particularly in the temporal region, obviously greater on the left. An isotope gamma scan showed a focus of increased uptake in the left hemisphere. Left carotid angiography (fig. 3) revealed a superficial left frontal arteriovenous vascular malformation, anterior to the ascending frontal gyrus, on F2. The dilated afferent arteries were anterior branches of the left middle cerebral artery; the malformation was drained by two dilated veins, running into the superior longitudinal sinus. Further selective angiography was performed through the femoral artery under general anaesthesia. The two anterior cerebral arteries and their branches, the meningeal branches of the left external carotid and the left posterior cerebral artery were normal and were not involved in supplying the malformation. The other

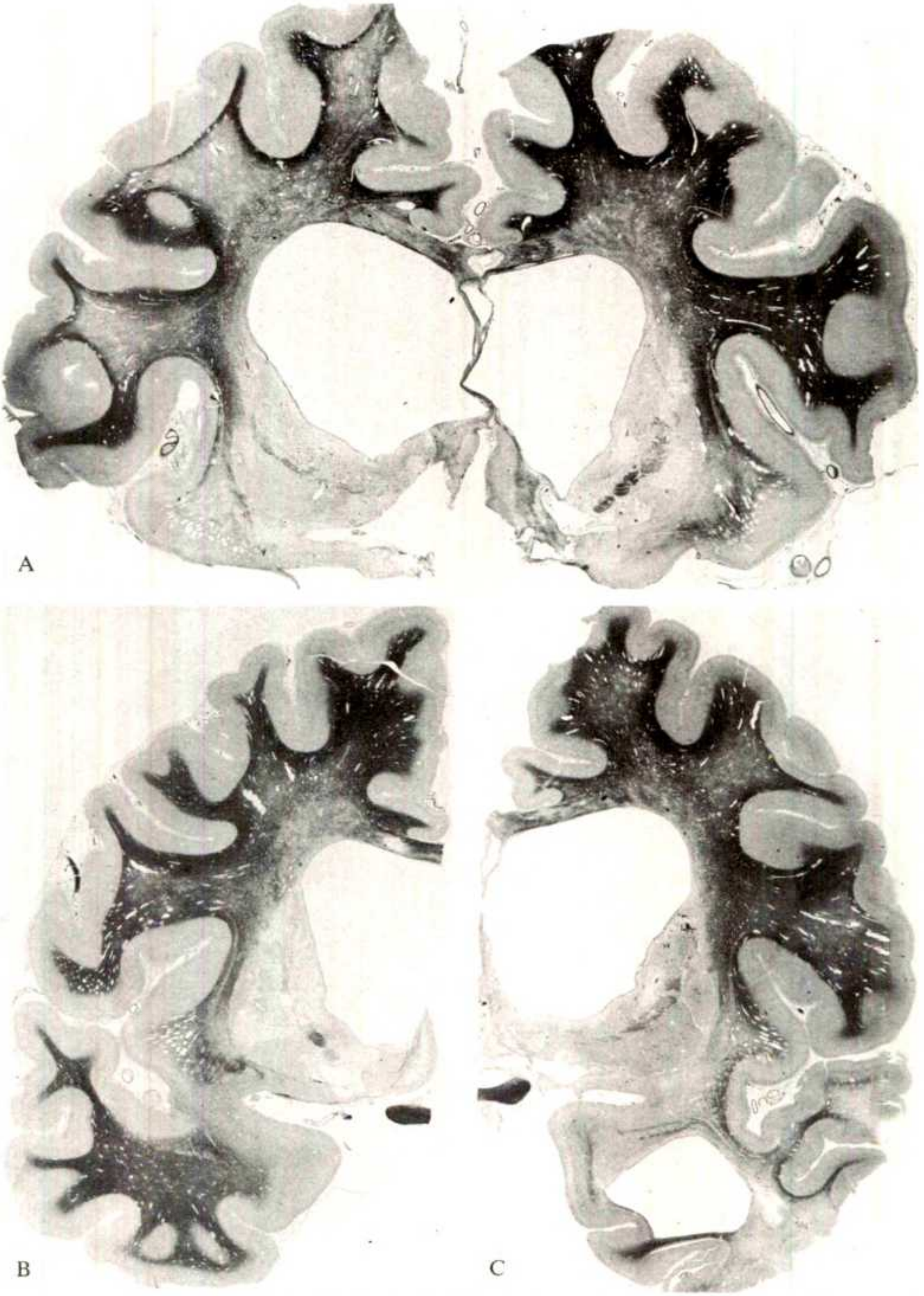

FIG. 2. *Case 1.* A, coronal section of frontal lobes ventral to the foot of F_3; bilateral infarction of the territory of Heubner's artery; old haematoma of the medial part of the corpus callosum; bilateral demyelination of the white matter. B, coronal section of the left frontal lobe, through the foot of F_3 and the optic chiasma. C, coronal section of the right frontal lobe at the same level as above.

cervical and intracranial arteries were normal. General clinical examination, haematology and CSF were normal.

The patient underwent a surgical procedure (Professor Pertuiset) on November 21, 1973. A superficial arterialized vein leading to the superior longitudinal sinus was ligated. The malformation was located at the bottom of a sulcus within the cerebral parenchyma, but did not reach the frontal horn of the ventricle. The draining veins, including a deep one, were clamped; the superficial arteries of medium diameter afferent to the malformation were ligated; the malformation was extracted, during which it was necessary for the surgeon to press strongly with the retractor on Broca's gyrus. Neuropathological examination of a fragment of the malformation revealed a delicate arteriovenous rete including haemorrhagic foci.

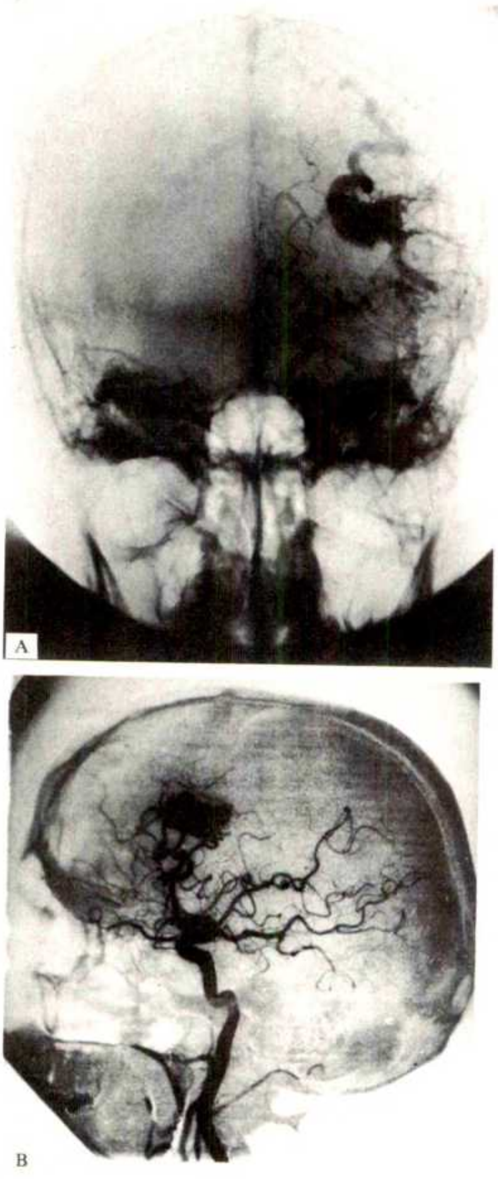

FIG. 3. *Case 2.* Left carotid angiogram (AP and lateral). Arteriovenous malformation.

Surgical intervention was followed by aphasia involving serious difficulties in verbal articulation. Speech utterance was reduced to certain phonemes: *pé*, *é*, *té* *ti*, *péi*. Oral comprehension and the execution of simple commands were clearly perturbed. Reading comprehension and writing to dictation were defective. A frontal syndrome also existed, with serious and bilateral disturbances of the Luria sequences of gestures, and grasping and utilization behaviour with both hands. The patient used a jug and a glass of water, a plate, a fork and an orange; he lit a candle with a match drawn from a box; he started writing with a fountain pen on a sheet of paper which he had grasped by himself. No sensory or motor abnormalities were apparent on the right side of the body except for a right central facial paralysis. The remainder of the neurological examination was normal. There was no sucking reflex.

The patient remained in hospital until March, 1974 for speech therapy. His difficulties in understanding rapidly disappeared; naming became possible but involved some verbal paraphasias, repetition was mildly impaired. Aphasia and manual grasping behaviour disappeared in the ensuing months. The patient was regularly examined by Dr J. L. Signoret until June, 1978. No neurological disorder was observed. The patient resumed a normal socioprofessional life, although he was given other employment in the Post Office, his history of seizures rendering him unsuitable for driving.

Case 3 (*No. 48.245*)

A right-handed skilled metallurgist presented for the first time on February 1, 1979, at the age of 48 years. For about six weeks he had suffered from left frontal headaches which had become bilateral; they usually occurred in the afternoon and were sometimes pulsatile. Neurological and general examination was normal, as was an EEG. Over the following months, the headaches became more persistent and the patient often vomited. At the same time, he noticed some difficulty with micturition (urgency sometimes leading to slight incontinence), and from time to time, weakness in both lower limbs. Neurological examination on March 18, 1981 revealed brisk knee jerks and bilaterally extensor plantar responses. There were no signs of frontal damage. Two CT scans (fig. 4A) demonstrated a tumour of the anterior part of the third ventricle, where the contrast appeared heterogeneous, and dilatation of the lateral ventricles due to bilateral occlusion of the foramena of Monro.

An operation was performed on March 26, 1981 (Professor Philippon). Access to the brain was by a wide right frontal approach, a 1 cm corticectomy on F_1-F_2 at 1 cm from the midline, opening of the lateral right ventricle and introduction of an operating microscope. An encapsulated grey-tinged tumour was present in the choroid plexus compressing the foramena of Monro. The tumour was removed in pieces, except for a small superior posterior fragment adhering to the choroid tela. Neuropathological examination (Dr Foncin) revealed the presence of old haemorrhagic foci containing crystals of cholesterol, part of the choroid plexus more or less modified, and granulomatous tissue containing haemosiderin and fibrovascular bundles. Conclusion: old haematoma with fibrous granuloma, probably related to a choroid plexus vascular malformation.

The patient's condition clearly worsened after surgery. He was again transferred to the Neurology and Neuropsychology Clinic on April 7, 1981, with an obvious right frontal syndrome. He showed considerable inertia and severe apathy, a left central facial paralysis, a slight left-sided motor deficit, and manual grasping

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Case 4 (*No. 58.654*)

A man aged 63 years with no previous history of cardiovascular disease suddenly developed a left hemiplegia during the night of October 1, 1981. He was admitted to the Neurology and Neuropsychology Clinic on the following morning. He was somnolent; his head and his eyes were permanently deviated towards the right; there was a complete left hemiplegia with sensory loss, the tendon reflexes were brisk on the left and the left plantar response was extensor. On being awakened, the patient showed anosognosia and left-sided neglect; his visual fields were full. The heart and neck vessels were normal, the pulse regular at 60/min and the blood pressure 170/120 mm Hg. The ECG was normal, as were haematological studies. Two Doppler examinations showed occlusion of the intracranial segment of the left internal carotid artery; right carotid and ophthalmic flow was not seriously diminished. A CT scan showed significantly reduced density in the right frontoparietotemporal region.

Over the course of some hours, consciousness improved. During the next few days, the patient became fully alert; he no longer suffered from anosognosia, his left-sided neglect improved, as did the paralysis of the left lower limb. On October 5, 1981, he could walk normally, whereas the left central facial paralysis remained severe and that of the upper limb total. His condition remained static in the following weeks. A further CT scan eleven days later (fig. 5) showed reduced density in the territories of the middle and anterior cerebral arteries with contrast enhancement.

At the beginning of November, only limited voluntary movement of the left shoulder and thumb was possible. Although not yet expected, it was easy to recognize manual grasping behaviour of the right upper limb, together with utilization behaviour (the patient had to be helped since he could only use his right upper limb). While seated, the patient took a glass, gave it to the examiner and then

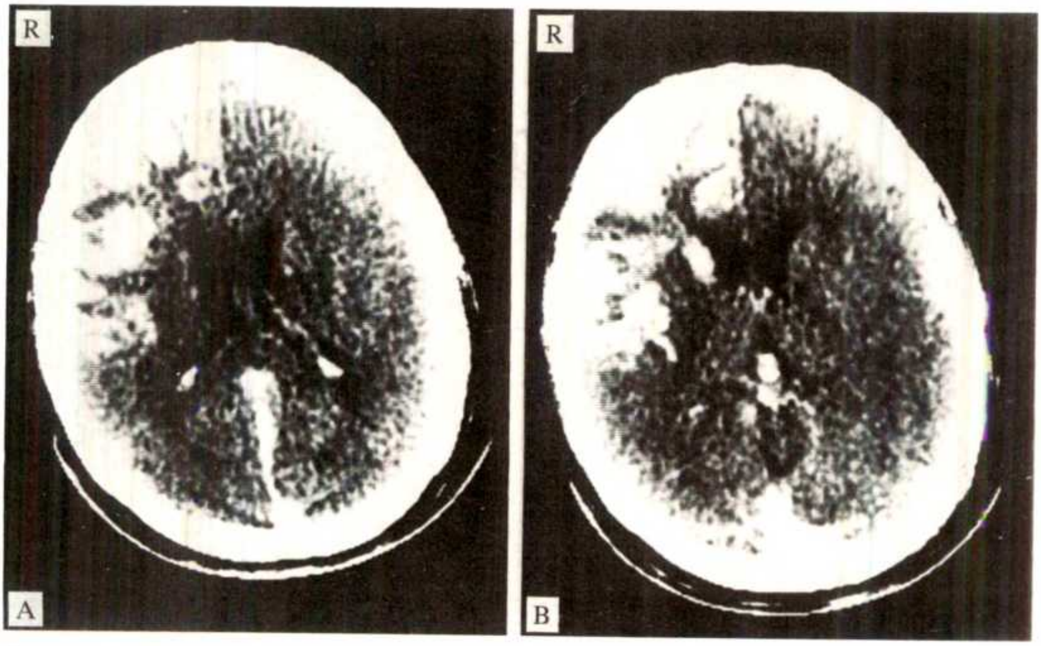

FIG. 5. *Case 4*. CT scan after contrast. A, at 71 mm showing enhancement of the medial face of the frontal cortex and second frontal convolution. B, at 62 mm same as above.

picked up a jug. He poured water into the glass and, having put down the jug, took the glass from the hand of the examiner and drank the water. Taking a pack of cigarettes, he hesitated a moment, then opened it and drew out a cigarette. He looked puzzled at it, being a nonsmoker. A few seconds later, he held it to the mouth of the examiner who accepted it and taking the lighter which was in the examiner's hand, near his knees, the patient lit the cigarette. Questioned on this behaviour, he simply said 'You held out objects to me; I thought I had to use them'. The patient left the Neurology Department on November 3, 1981 to continue his rehabilitation.

This patient has left-sided dominance for the lower limbs; he is right-handed, using the right upper limb for writing and for using everyday objects, drinking and eating, handling a rifle, shaving, brushing his teeth and dressing. All members of his family are right-handed.

Case 5 (No. 60.171)

A right-handed man aged 77 years, with no previous history of neurological disorder, began to have behavioural problems in February 1982. On February 17, 1982, when returning home in Paris, he got out at the wrong Metro station. On the following day, he left home for no reason at 5 p.m. and did not return that night. The next day his wife was notified that he was in a suburban café and was confused, mistaking a waitress for her, asking why he had not remained in a 'clinic' where he could see his daughter and grandchildren. During the next few days he had trouble walking, fell several times, and had episodes of urinary incontinence.

He was admitted to the Neurology and Neuropsychology Clinic on March 11, 1982. He was alert, was unstable walking, had a slight left hemiparesis and a left

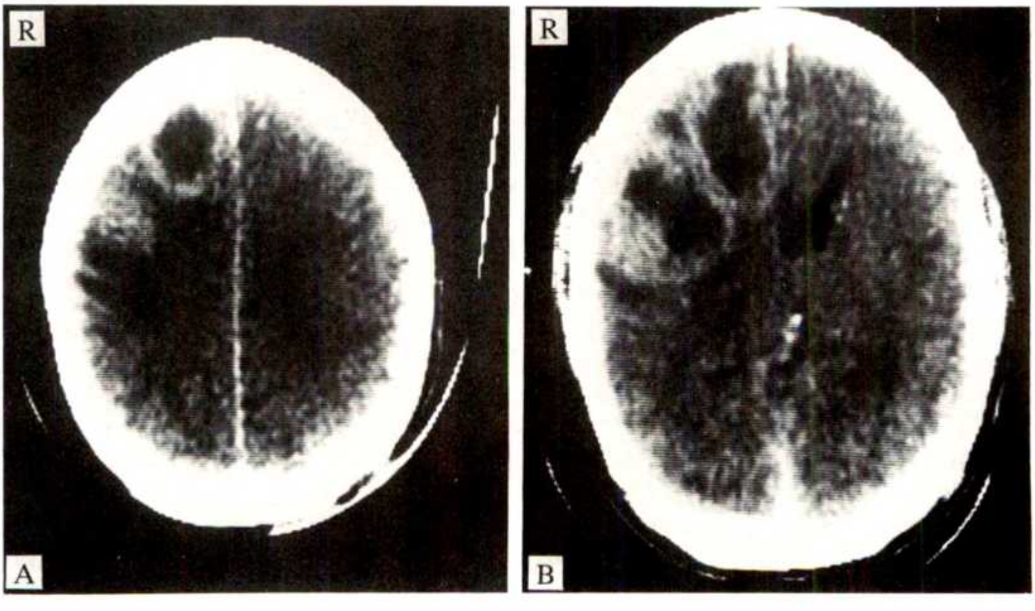

FIG. 6. *Case 5*. CT scan after contrast medium. A, at 80 mm showing the right frontal glioma. B, at 53 mm, same as above.

extensor plantar response. He was disorientated in time and space, neglected the left when drawing or writing, made errors when copying a cube and when locating cities on the map of France. Language was normal. In conversation his judgement seemed normal. Bilateral manual prehension was so intense that when the observer had him take hold of his left forearm with the other hand, it was almost forced grasping. With objects, bilateral utilization behaviour was evident (*see* fig. 8) and was observed with a glass and carafe of water, with bread, with three pairs of glasses that he placed on his nose, one on top of the other, with a sheet of paper and an envelope, and with a urinal which he placed between his thighs while trying with the other hand to insert his penis. There was no sucking reflex when his lips were stimulated with a finger.

A CT scan performed on March 11, 1982 (Professor Bories) revealed a glioblastoma which extended throughout the whole right frontal lobe (fig. 6). The patient was discharged six days later and returned home.

METHODS AND RESULTS

Normal Subjects

The subject and the examiner are seated face to face. The subject has received no information about the test. The test requires absolute silence on the part of the examiner and those around him (whatever their number) so as to give no encouragement which might be understood as an order. At no time does the examiner speak, even if the subject asks him a question. His eyes are fixed on the subject's hands and on the objects presented to him. The test begins with the solicitation of manual grasping behaviour: the examiner places his hands on the subject's palms and stimulates them with repeated slow and/or brisk movements. The subject (always) lays his hands out more or less flat with the fingers extended. The stimulation may be continued for 30 s or more without the subject ever manifesting grasping behaviour. The examiner stimulates in the same manner, but using an object, one of the patient's hands; then, with another object, both hands. The test continues with objects the subject might be expected to take and use (such as a pack of cigarettes, lighter, carafe, dish, fork, knife, fruit, bread). The examiner repeats the stimulation on the palms, the fingers and near the hands. He can hold out the objects and withdraw them abruptly as if he wanted to incite the patient to seize them. The hands of the subject remain constantly supine and immobile and never grasp the object. If the examiner releases the object which is stimulating the palm, it is very rare that the subject will grasp it to keep it from falling. In our experience, the normal subject makes no comments; rarely he asks 'What do you want me to do?' In this case the examiner does not respond and continues the test as if he heard nothing without modifying his gaze which remains fixed on the subject's hands. In no case does grasping behaviour appear. The same test can be performed with a table placed between the examiner and the subject. The result is the same. Questioned about these stimulations, the responses hardly vary 'You touched my hands with your hands, with a glass and a carafe, then with a pack of cigarettes and a lighter.' The examiner continues to question 'Yes, but why?' The subject answers with hesitation 'I thought you wanted to know if I could feel the objects'; 'You examined the sensitivity of my skin'; 'You were probably looking for something, but I don't know what'; or 'I don't know.' A last important point: at any moment in logical or absurd situations (suddenly in the middle of a sentence) if the examiner holds out his right upper limb and his hand as if to shake hands, at least all French subjects respond to this gesture by shaking hands with the observer. In the same way, if in the course of a conversation, the examiner rises at the end of a sentence, in almost all cases, normal subjects will rise understanding that the conversation is over.

When the initial study was first presented orally at the Société Française de Neurologie in 1981, we began to examine a member of the audience selected at random. This person behaved like any normal subject.

Patients with Utilization Behaviour

The test begins with manual grasping behaviour. The examiner places his hands in the hands of the patient to get him to rise, to take a few steps, to sit down again. Short visual-manual stimulations are repeated with the objects by withdrawing the object quickly as in play. The objects are then shifted within the field of vision, far away from the patient's hands, which incites the patient to make a large gesture with one of his upper limbs in order to grasp them.

The hands of the patient being free, the examiner then shows a utilitarian object—a glass, for instance—within the field of vision of the patient, which he then brings within reach of one of the patient's hands. The patient grasps the object. The examiner then holds a bottle of water towards the other hand under the same conditions (fig. 7A, B). The patient naturally grasps it. Usually, the patient remains more or less puzzled; often, his eyes seem to question the examiner. This phase lasts up to 15 s. The patient then pours the water from the bottle into the glass which he raises to his mouth and drinks (fig. 7A, B). The examiner presents a new object—an orange or an apple, for instance—in the field of vision, more or less in the vicinity or within reach of a hand which grasps it; he then presents a knife and a plate. The patient puts the plate on a table, peels the fruit and eats it normally. After a few tests, the visual stimulation is sufficient and often the patient grasps and uses the objects without any hesitation. The test can be performed with a multitude of objects provided that one of them is necessary in order to use the other (figs. 7 and 8) (hammer and nail; butter, knife and bread; cheese, knife and bread; plate, fork, knife and piece of cake; envelope and sheet of paper). With a fountain pen and a sheet of paper, the patient puts the latter on a table, removes the cap of the pen and starts writing his name or that of the hospital or the beginning of a sentence. The patient puts on three pairs of glasses and at the end of this test wears all three. If the patient is a smoker, he draws a cigarette from the pack and lights it with a lighter (fig. 7E, F). If he is a nonsmoker, he uses neither the pack of cigarettes nor the lighter, but if the examiner brings a cigarette to his own lips, the patient kindly lights it with the lighter

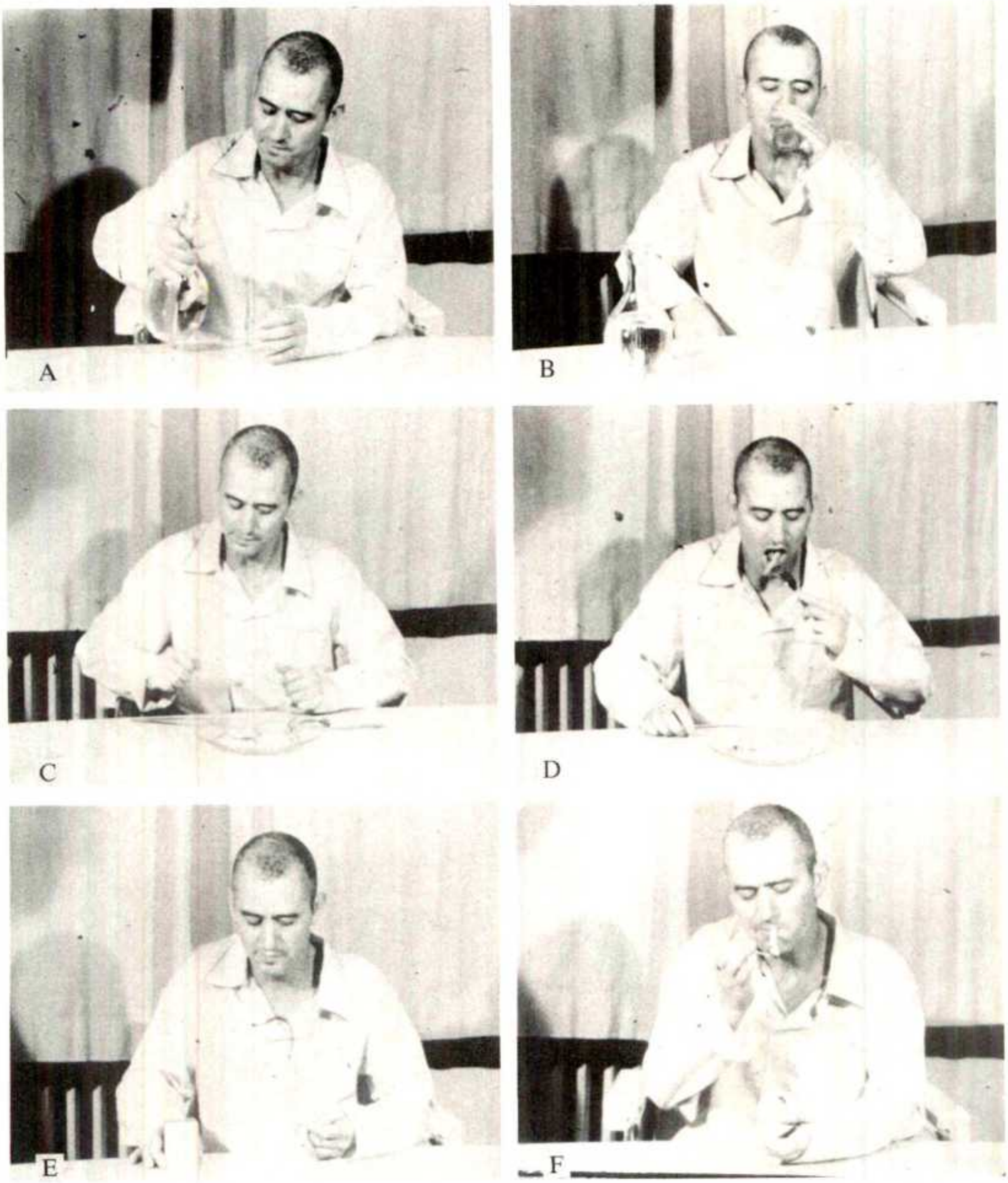

FIG. 7. Examples of utilization behaviour in *Case 3* (extracts from a film). A, B, drinking behaviour. C, D, eating behaviour. E, F, smoking behaviour.

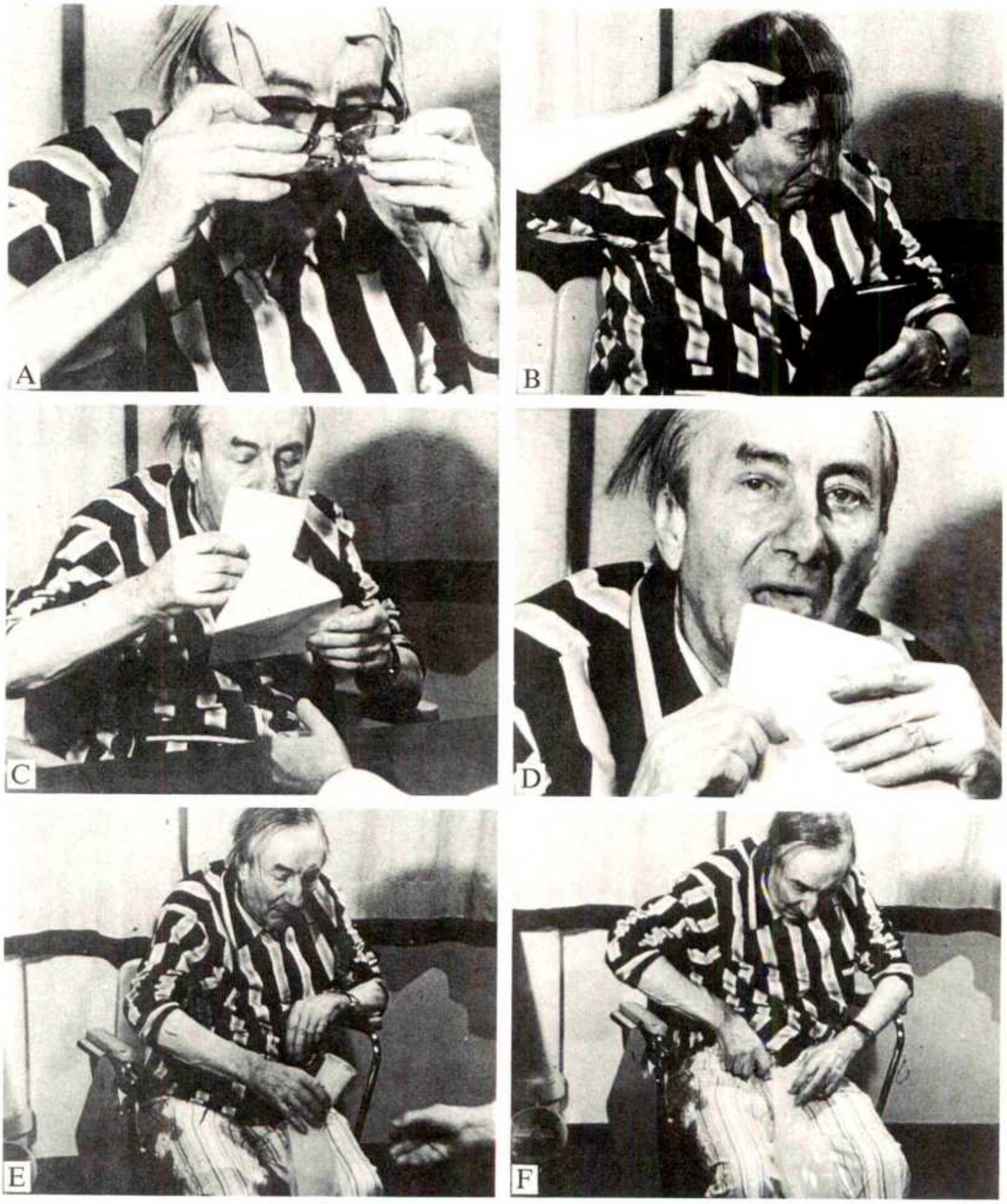

FIG. 8. Examples of utilization behaviour in *Case 5* (extracts from a film). A, putting glasses on his nose. B, combing his hair. C, D, folding paper and putting it in an envelope. E, F, using the urinal.

that he holds in one hand. Sometimes the patient draws a cigarette from the pack and offers it to the examiner, then he lights it with the lighter. The only object that patients never use, except for one instance (fig. 8E, F) is the urinal. It must be admitted that this object plays a special part in human behaviour as it involves at once a physiological need as well as a social inhibition.

If the examiner asks the patient why he grasped the objects and used them, the answer is always the same 'You held them out to me, I thought I had to use them.' The examiner can try to object to this behaviour 'I didn't tell you anything nor ask you for anything.' Or he gives repeatedly and even brutally this order 'You are mistaken; from now on, don't grasp any of the objects I will show you; and in no case must you use them.' After about 20 to 30 s. during which the patient's attention has to be diverted, the examiner begins the test again with the same objects or with others.The behaviour remains unchanged. If then the examiner pretends to be surprised that the patient should have forgotten his order, the latter replies most of the time 'It's true, I remember.' 'Then why?'. 'Because you held out the objects to me and I thought I had to grasp and to use them.' These exercises can be repeated, the same behaviour recurs regularly. Only a few patients respected the order not to grasp or use the objects. In some cases, the behaviour is more variable. Numerous patients grasp 2 or 3 utilitarian objects then ask the examiner 'Must I use them?'. The examiner does not answer. The patient, after a short time, repeats his question which receives no reply. The patient keeps the objects in his hand without any limit of time until the examiner holds out his own hand, which incites the patient to hand the objects over to him.

No patient suffering from cerebral lesions that did not damage the frontal lobes exhibited this utilization behaviour.

DISCUSSION

Utilization behaviour of this type has not so far been reported. Somewhat similar behaviour was observed by Bancaud *et al.* (1976) in their study on electrical stimulation of the anterior part of the cingulate area (area 24) (83 epileptic patients; 521 stimulations). Only one patient drew a cigarette from the pack, brought it to his mouth and lit it. These authors did not emphasize this fact and have shown that electrical stimulation of this region induced the reappearance of primitive manual and buccal behaviour. Such behaviour has nothing in common with the behaviour described here. A case of complex behavioural disturbance was reported by Laplane *et al.* (1981) related to bilateral necrosis of the rostral part of the corpus callosum and of territory of Heubner's artery. A 'compulsive' psychomotor behaviour was observed in the patient, together with memory defects and difficulties with attention. 'The patient seized the object and used it properly as if it was a normal thing to do.' This behaviour was considered to result from regression to primitive behaviour. Our patients had no compulsive behaviour; they simply took and used the objects presented to them, often with hesitation, always with a slow or normal temporal rhythm.

There has been renewed interest in unilateral forced manual grasping since Denny-Brown suggested (1956, 1958) that this motor activity reflected a modification of space exploratory behaviour. In the monkey, Denny-Brown and Chambers (1958) showed that this behaviour is organized within the parietal cortex and that it is released by lesions of the frontal cortex; inversely, the functions organized within the frontal cortex control and inhibit parietal activity, hence the appearance of repellent behaviour after parietal lesions. Later, Hyvärinen and Poranen (1974) showed that in monkeys, the movement is 'initiated' in the parietal area before being 'performed' in the motor zone. The frontal lobe is presumed to inhibit the parietal lobe. Denny-Brown (1956, 1958) applied this hypothesis in human behaviour after frontal lesions. 'We believe that the two types of responses represent two areas of normal organisation, positive and negative, of the tropism to the environment managed by the cerebral cortex. Damage to the mechanism of either one releases abnormal activity of the other' (Denny-Brown, 1958). Moreover, he pointed out that this activity concerned only the side of the body contralateral to the cerebral lesion, with the exception of cases in which the frontal lesion was very severe.

Denny-Brown (1958), in equating human brain function with that of the monkey, reduced this behaviour to an elementary sensorimotor level. This interpretation does not fit with the behaviour described in this study. (1) Manual grasping behaviour is bilateral; it is observed with bilateral and unilateral lesions of frontal lobes. (2) Utilization behaviour is also bilateral and is observed in the same kinds of lesions; it is a more severe form of manual grasping behaviour and never appears by itself. In these cases, tactile, visual-tactile, or visual stimuli imply to the patient an order *to grasp the objects presented and to use them.* Observation of the behaviour of these patients is instructive in this respect: the stage when they hesitate and do not use the grasped objects; the stage when, after a moment of hesitation, they use them; the stage when, without hesitation, they use them at once. The verbal comments of the patients when they are questioned confirmed this categorically. We never heard a normal subject or one in which the frontal lobes were intact asking whether he had to use these objects (only, rarely, 'What do you want me to do?'). The contrast is striking when considering another stimulus, offering one's hand to shake. This stimulus is so powerful that all subjects, normal and pathological, respond to it in all situations. Another gesture which has identical value is rising at the end of a sentence in a conversation taking place between several seated persons and, in the past, a third gesture had similar power, greeting a person met in the street by removing one's hat.

A last point, no suction behaviour was observed in the four cases with unilateral lesions of the frontal lobe. Denny-Brown (1958) observed it but he used a spoon as a stimulus (1958, fig. 3A, B). In this case, the behaviour was adapted to the stimulus and was not related to the release of a reflex of automatic suction which can be provoked by nonsignificant stimuli (such as the finger or a tissue).

We believe that the interpretation of Denny-Brown (1956, 1958) of an imbalance between the activities of the frontal and parietal lobes must be interpreted at a higher than purely sensorimotor level which involves the entire activity of the brain. It can be expressed as follows. All the information coming from the body and from the outside world is received in areas of the sensory cortex which surround the parietal lobe; systems develop in the parietal area which unite these unending sequences of stimuli. These systems activate other unknown patterns, material counterparts of their meaning, and prepare the response of the patient. The result is that the normal activity of the parietal lobe tends to create links of dependence between the subject and stimuli from the environment, while some of the functions of the frontal lobe allow the subject to remain aloof from the outside world and to ensure his independence by modulating and inhibiting the activities of the parietal cortex. With normal subjects the balance between these two activities is fluid so that the subject's behaviour is more or less dependent or independent of the outside world as a function of the quality of the external stimuli and internal mental activity. Frontal damage suppresses to varying degrees this function and thus releases the activity of the parietal lobe, that is, it tends to subject the patient to all external stimuli.

It must be stressed that the programme for the gesture is performed without any *internal motivation*. Patients eat even after their lunch, drink without any need, smoke, write or use the urinal (Case 5) in the same conditions. Without any food, the patient (Case 1) replicated the gestures of cutting with a plate, a knife and a fork.

This interpretation incites us to reject the terminology of magnetic apraxia suggested by Denny-Brown (1958). The meaning of 'magnetic' is strictly limited to physics, but the metaphor has its charm. The word 'apraxia' is incorrect. The so-called kinetic, ideomotor, and ideational apraxias belong to the organization of gestures, starting from the most elementary sensorimotor levels, up to the most elaborate levels, namely, symbolic and semantic. This field is related to, but different from, that which in the subject's brain makes him more or less dependent on external stimuli. It is better to refer to it as 'manual grasping behaviour'.

In consequence, we questioned whether lesions of the parietal lobes were not able to induce 'indifference' or even 'escape' behaviour, in response to tactile, manual, visual-tactile or visual stimuli which are more elaborate than the repellent response. However, we have never observed this except for the usually left-sided body and space neglect, which can exceptionally be seen on the right. This disturbance is quite different from utilization behaviour.

Like manual grasping, utilization behaviour is frequent in presenile degenerative diseases, in particular Alzheimer's disease, but it can be seen in other types of bilateral frontal lesions. It can also be observed with both hands after lesions unequivocally limited to the left or the right frontal lobe. But it is certainly far less frequent. We cannot give an objective estimate of its frequency in unilateral frontal lesions.

Denny-Brown (1958) has studied anatomical cases of unilateral 'magnetic apraxia' with lesions of the medial part of the frontal lobe (tumour or occlusion of anterior cerebral artery), 'but the lesion was too extensive for exact anatomic analysis'. On the basis of the five observations presented in this paper, it also seems difficult to define precisely the frontal structures responsible for this behaviour. In Case 2 (fig. 3) an arteriovenous malformation was situated unquestionably in the corticosubcortical premotor area of the external face of the frontal lobe; but the frontal syndrome and utilization behaviour were only observed subsequent to surgical intervention. It is thus certain that the intervention caused other frontal lesions. According to the CT scanning images for Cases 3, 4 and 5 (figs. 4B, 5 and 6), the lesions affected the medial surface, the orbital surface and the anterior pole of the frontal lobe (in Case 3, the lateral face of the frontal lobe was quite normal). More precise data are provided by the neuropathological study in Case 1 (figs. 1 and 2). The lateral and medial cortex of the frontal lobes were normal; only the white matter of the centrum ovale was demyelinated (secondary degeneration to the haemorrhagic and necrotic foci in the anterior part of the corpus callosum). In these conditions, it is probable that the cortex of the medial and lateral surfaces of the frontal lobes do not play a role in the liberation of the manual grasping and utilization behaviour. Lesions of the anterior part of the corpus callosum were not involved (the central and posterior parts of the corpus callosum were normal). The lower frontal pole, the orbital surface of the frontal lobes and the region of the Heubner's artery (in particular, the caudate nucleus) were necrotic. The role of the caudate nucleus is problematic, since it is connected by large fascicles to the orbital and medial areas. The pole and the orbital surface of the frontal lobe have a strong influence on motoricity (ascending and premotor frontal gyrus; deep grey nuclei), but also on many other corticosubcortical areas of the brain. These lesions may therefore be responsible for the manual grasping and utilization behaviour. It might thus be admitted that utilization behaviour, together with the other frontal symptoms, decreased three-and-a-half months after the operation and were not present at the time of the neuropathological examination. It is not possible to define more accurately the exact sites of the lesions in the frontal lobe responsible for the release of this pathological behaviour. The question arises as to whether such behaviour emerges when disturbances of frontal lobe function are induced by deep lesions of the brain (especially of the thalamus). We have not so far observed such a case, but this possibly cannot be excluded.

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COGNITIVE DEFICITS IN THE EARLY STAGES OF PARKINSON'S DISEASE

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SUMMARY

Neuropsychological tests known to reveal abnormalities in patients with frontal lobe damage were used to explore cognitive function in 30 mildly disabled, right-handed patients with idiopathic Parkinson's disease. None of the patients had received treatment and all had normal CT brain scans. Patients with depression or high ischaemia scores were excluded from the study and similar selection criteria were used for the age-matched controls. No impairment of general intellectual function was found in the patients using the WAIS and New Adult Reading IQ tests and no abnormalities were apparent on cognitive estimates and two-choice Recognition Memory Tests. Patients with Parkinson's disease, however, had significantly greater difficulty in shifting conceptual sets and produced more perseverative errors on both the modified Wisconsin Card Sorting Test and Benton's Word Fluency Test. These subtle cognitive difficulties might underlie the mental inflexibility and rigidity of Parkinson's disease and could be attributed to destruction of the ascending dopaminergic meso-corticolimbic pathway.

INTRODUCTION

Charcot and Vulpian (1861) first drew attention to the occurrence of mental changes in Parkinson's disease and in his later lectures at the Salpêtrière, Charcot emphasized that 'at a given point the mind becomes clouded and the memory is lost' (Charcot, 1875). Ball (1882) described seven patients with psychiatric symptoms one of whom was probably demented and Walshe (1955) was also of the opinion that many parkinsonian patients become intellectually impaired. More recently, generalized cognitive deficits have been confirmed in Parkinson's disease using a battery of different neuropsychological tests on large numbers of unselected patients (Warburton, 1967; Reitan and Boll, 1971; Celesia and Wanamaker, 1972; Loranger *et al.*, 1972). Quoted prevalence figures for dementia range from 3 to 50 per cent (Mjönes, 1949; Pollock and Hornabrook, 1966; Marttilla and Rinne, 1976; Sweet *et al.*, 1976; Lieberman *et al.*, 1979; Shaw *et al.*, 1980), all the higher figures having been reported in the last ten years. It is uncertain, however, whether improved life expectancy, a deleterious long-term effect of L-DOPA or simply greater awareness on the part of clinicians is responsible for this apparent change. In most of the currently available literature, in fact, it is impossible to disentangle the relative contributions of depression, medical and surgical treatment, cerebrovascular disease and normal ageing, and while most physicians would now accept intellectual impairment as a common late sequel of Parkinson's disease, not all would consider dementia part of the primary symptom complex.

Two main theories have been proposed to explain the frequent occurrence of dementia in Parkinson's disease. Rossor (1981) has put forward the notion that Parkinson's disease and Alzheimer's disease may be two parts of a spectrum of disease caused by loss of neurons within the isodendritic core. The cells of the substantia nigra, locus coeruleus, substantia innominata and septal nuclei all share a nonspecialized dendritic pattern which forms a continuous network from spinal cord to forebrain. Dense intertwining of these structures with adjacent axons and dendrites is a characteristic feature and it has been suggested that this cell core may represent a phylogenetically ancient pool of relatively undifferentiated neurons (Ramon-Moliner and Nauta, 1966). A biochemical susceptibility to premature ageing or a particular vulnerability to an as yet undetermined environmental injury could lead to selective neuronal loss; this in turn might cause secondary degeneration of cells in the corpus striatum in Parkinson's disease and in the cerebral cortex in Alzheimer's disease. Support for this hypothesis comes from the clinical (Pearce, 1974; Drachman and Stahl, 1975), histological (Forno *et al.*, 1978) and neurochemical (Adolfsson *et al.*, 1979; Cross *et al.*, 1981) overlap between the two diseases in their terminal phases. In a clinicopathological study, all nine parkinsonian patients who had been severely demented showed histological changes in the cerebral cortex indistinguishable from those found in Alzheimer's disease (Boller *et al.*, 1980). A reduction in choline acetyltransferase (ChAT) activity, similar to that found in Alzheimer's disease, has also been found in the substantia innominata and the cerebral cortex of demented parkinsonians (Ruberg *et al.*, 1982). Furthermore, cortical atrophy can be demonstrated radiologically in some patients with Parkinson's disease (Selby, 1968; Sroka *et al.*, 1981).

In contrast to Alzheimer's disease, severe agnosia, apraxia and language disturbances are unusual and most patients retain insight into their diminishing mental faculties. In many ways their cognitive deficits more closely resemble those seen after certain types of frontal lobe damage (Bowen, 1976) and also share similarities with the difficulties experienced by normal old people (Albert, 1978). Several studies have found a direct correlation between the degree of intellectual impairment and the severity of bradykinesia in Parkinson's disease, the relationship holding even when age, age at onset and self-rated depression are controlled (Mortimer *et al.*, 1982). Albert (1978) has therefore propounded an alternative hypothesis which states that damage to the basal ganglia and its intimate connections with the frontal lobes and limbic system might cause a specific 'subcortical dementia'.

In the first few years of the illness most patients with Parkinson's disease have no difficulties in perceiving, learning, remembering or understanding. Many continue in intellectually demanding jobs, are able to enjoy good music, compose poetry and appreciate stimulating conversation. Nevertheless subtle changes may be apparent to those closest to them. A slight lack of spontaneity, an increasing poverty of imagination and a tendency to repetition may lead to considerable difficulties in sustaining repartee. Patients sometimes complain of mild forgetfulness, tiredness and occasionally of losing their way in unfamiliar surroundings. Inertia is another common symptom which causes lack of initiative and an air of mystical impassivity. Schwab *et al.* (1954) noted that many patients had difficulty in attending to more than one motor act at the same time. All these difficulties are intermittent and may be corrected temporarily by will power on the patient's part or by external exhortation.

In patients with early idiopathic Parkinson's disease, damage to the brain is probably largely confined to the ascending central dopaminergic pathways, the hypothalamus and the locus coeruleus. Destruction of the nigrostriatal dopaminergic bundle profoundly disrupts basal ganglia function and, as Marsden (1980) has indicated, careful study of mild or moderately disabled parkinsonian patients may help to unravel some of the enigmas which surround the function of the basal ganglia.

In an attempt to examine the putative role of the basal ganglia in cognition, we have studied a group of mildly disabled, young, untreated patients with idiopathic Parkinson's disease using a selection of psychological tests known to expose deficits in patients with frontal lobe syndromes.

PATIENTS AND METHODS

All newly diagnosed patients with idiopathic Parkinson's disease seen between January 1979 and December 1981 were included in the study provided the following criteria were met: (1) 65 years of age or under; (2) predominantly right-handed (Edinburgh Handedness Inventory, Oldfield, 1971); (3) normal CT brain scan; (4) no evidence of depression based on clinical impression and the Zung self-rating scale (Zung, 1965); (5) an ischaemia score of less than 4 (Hachinski *et al.*, 1975); and (6) no exposure to antiparkinsonian medications.

Nineteen patients failed to meet these requirements, 11 because of their age, 3 because of left-handedness, 2 because of depression, 2 because of a high ischaemic score and evidence of cerebral infarction on CT brain scan and 1 because of moderate cortical atrophy. The 30 eligible patients comprised 19 males (mean age 59.4 years, SD 6.8) and 11 females (mean age 58.0 years, SD 7.9). The mean duration of disease from first symptom was 2.4 years (range 6 months to 5 years) and most were mildly disabled. On the Hoehn and Yahr scale, 12 patients were stage 1, 13 stage 2 and 5 stage 3 (Hoehn and Yahr, 1967). In those patients with predominantly unilateral disease, 10 had mainly right-sided disabilities and 13 left-sided.

Thirty age-matched controls were chosen from hospital inpatients without brain damage. The large majority were in hospital waiting for elective surgery for prolapsed intervertebral discs or carpal tunnel syndrome. The selected controls had no evidence of depression on the Zung scale and all had ischaemia scores below 4. They comprised 17 males (mean age 56.1 years, SD 9.7) and 13 females (mean age 51.0 years, SD 10.1).

Neuropsychological Tests

All the tests were carried out in a quiet well-illuminated room.

Wechsler Adult Intelligence Scale (*WAIS*) (*Wechsler*, 1958). This is the best standardized and most widely administered test of general intelligence. The verbal subtests with the exception of arithmetic and digit span mainly require the simple retrieval of previously acquired knowledge, whereas the performance tests require perceptual analysis, organization and acquisition of new and unfamiliar material. Arithmetic, similarities, digit span and vocabulary subtests were carried out on the verbal scale and digit symbol, picture completion, block design and picture arrangement on the performance scale.

New Adult Reading Test (Nelson and O'Connell, 1978). This test is based on the observation that word-reading ability and general intelligence level are significantly correlated. Relative preservation of word-reading occurs in patients with dementia and as a consequence reading tests have been used as indications of premorbid intelligence. In this test subjects are asked to read aloud 50 words chosen to assess word familiarity rather than ability to decode phonetically unfamiliar words by intelligent guesswork.

Modified Wisconsin Card Sorting Test (Nelson, 1976). The modified Wisconsin Card Sorting Test is an adaptation of the test first devised by Grant and Berg in 1948 and measures the ability to develop new concepts and shift sets. It also requires the subject to suppress a previously correct response and produce a new one. The original test as employed by Milner (1963) consists of 4 stimulus cards each of which is unique in terms of its colour (red, green, blue or yellow), shape (triangle, star, cross or circle) and number of items (one, two, three or four). The response cards comprise 2 sets of 64 cards with all possible combinations of the colour, shape and number. The subject is required to place each response card below a stimulus card in the position he thinks it fits best. After each response he is told whether this was right or wrong with no other cues given at any stage. The subject must first match for colour and, after 10 correct responses, switch without warning to shape and then number. The modified Wisconsin test has the same stimulus cards but all cards sharing more than one attribute with a stimulus card (for example, same colour and same shape) are eliminated leaving a 24-card set which is then duplicated. This has the advantage of removing certain ambiguities and gives a clearer view of which strategy the patient is using.

The instructions given to the patient are as follows. 'Here we have 4 key cards. I want you to sort these cards (indicating the response cards) under the key cards according to certain rules, but the whole point of the test is that I shall not tell you what the rule is. I want you to find out by trying different rules and each time I shall tell you whether it is right or wrong. Now go ahead and find out the rule.'

Following these instructions, whichever category was chosen by the subject was scored correct and subsequent responses scored accordingly. After 6 correct responses in a row the patient was told that the rule had changed and that he must find another rule. This instruction was then repeated each time the rule was changed.

Assessment of overall proficiency on the test was judged by the number of categories achieved (maximum 6) and the total number of errors made. In addition, in those patients who failed to complete the test, an analysis of the type of error made (perseverative or nonperseverative) was carried out. Using Milner's classification an error was scored as perseverative if it followed the category concept which had previously been correct. Nelson's modification consists of an error being regarded as perseverative if it followed the same category concept as the immediately preceding response. This alteration in scoring was based on the observation that many patients rapidly forgot which category concept had previously been correct and that a sudden return to the previous concept was not necessarily indicative of perseveration. Experience with the modified Wisconsin Card Sorting Test at the National Hospital for Nervous Diseases has shown it to be more suitable for use with elderly patients, who often fail to grasp what is required in the full test and become bewildered and distressed.

Two-choice Recognition Memory Tests for Words and Unknown Faces (Warrington, 1974). Both these tests involve the presentation of 50 stimulus items presented at 3 s intervals. The words are all 4 to 6 letters long and of high frequency and the unknown faces were all unfamiliar male actors selected from *Spotlight* magazine. The subject is required to read each word aloud and with the faces answer yes or no according to whether he or she liked the look of the actor. Recognition was tested without delay immediately after the presentation of the test stimuli, the paired distractor item being drawn from the same total pool as the test items. A maximum total correct score for each test of 50 was given. Deficits on this test are most usually associated with temporal lobe damage.

Cognitive Estimates Test (Shallice and Evans, 1978). Based on the clinical observations that failure of judgement and difficulty in dealing with novel situations is common in patients with frontal lobe damage, 10 key questions were designed. All these can be answered using general knowledge available to almost all subjects but for which no immediately obvious strategy is available. Answering depends on intact comprehension, selection of an appropriate cognitive plan, execution of the strategy and then checking any putative answer. Limited arithmetical competence is also required for some questions. The following instructions are given. 'Would you please make the best guess you can in answer to each of these questions. Almost certainly you will not know the exact answer, for instance, the height of a double-decker bus is 14½ feet but a reasonable guess would be anything from 12 to 18 feet.' Patients are given as long as they want and the question may be repeated. A scaled score from 0 (correct) to 4 (wildly inaccurate) is given for each question.

Word Fluency Test (Benton, 1968). Subjects were instructed to name as many words beginning with the letter D as they could in 1 min. Peoples' names and proper nouns were not permitted. The letters B and M were then presented successively, 1 min being used for each test. Scores for each letter were analysed separately. The number of perseverative errors were scored separately.

The data were analysed using SPSS Version 7.0 on the University of London CDC 6600 computer. The Mann-Whitney U 2-tail test was used to compare patients and controls.

RESULTS

The patients and controls did not differ significantly in their performance on the WAIS and Adult Reading IQ Tests (*see* Table 1). Separate analysis of the individual subtests of the WAIS also revealed no differences.

TABLE 1 WAIS AND READING TEST IQ SCORES

	Patients weighted means (SD)	*Controls weighted means* (SD)	*P*
WAIS Verbal IQ	108.9 (9.8)	108.8 (8.8)	n.s
WAIS Performance IQ	103.3 (11.7)	107.4 (10.3)	n.s
Reading IQ	110.5 (8.8)	111.0 (9.3)	n.s

Significantly fewer categories were completed by the patients on the Modified Wisconsin Card Sorting Test ($U = 318.5$, $Z = 2.07$, $P = 0.03$), although the difference in the total number of errors did not reach a level of significance ($U = 537$, $Z = 1.3$, $P = 0.19$). Only 11 (37 per cent) of the patients completed the test compared with 17 (57 per cent) of the control subjects (*see* fig.). Separate analysis of the quality of errors was considered to be inappropriate in those subjects who were able to finish it. In the test failures, however, the parkinsonian patients produced significantly more perseverative errors than controls using the Milner method of classification ($U = 585$, $Z = 2.02$, $P = 0.04$); 56 per cent of all errors were perseverative compared with 33 per cent in the controls. Furthermore in 11 of the 19 patients who failed to complete the test, the percentage of perseverative errors

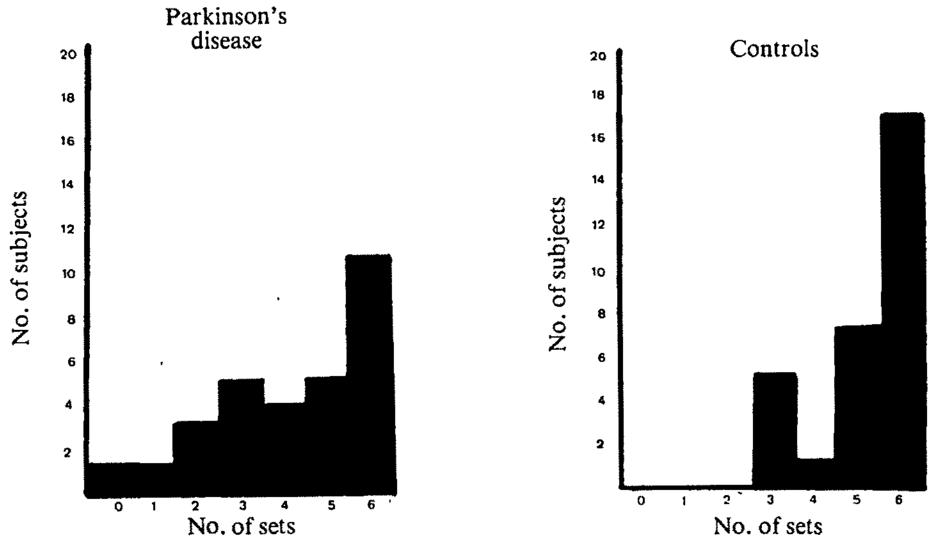

FIG. Histograms comparing the number of sets completed on the Wisconsin Card Sorting Test in patients and controls.

was more than 50 per cent of the total number of errors (compared with 4 of 13 controls). Using Nelson's method, a similar trend towards more perseverative errors in the patients occurred but this did not quite reach statistical significance ($U = 570$, $Z = 1.8$, $P = 0.07$) (*see* Table 2).

TABLE 2. TYPES OF ERROR ON WISCONSIN CARD TEST

	Parkinsonians' mean (SD)	*Controls' mean (SD)*	*P*
Total errors	17.0 (6.0)	15.2 (5.0)	n.s.
Perseverative errors (Milner classification)	9.6 (6.2)	5.1 (3.5)	< 0.05
Perseverative errors (Nelson classification)	6.3 (4.7)	3.8 (2.7)	n.s.

No difference was found between patients and controls on the cognitive estimates test. The mean scaled score was 4.4 (SD 3.7) in the patients and 4.1 (SD 2.3) in the controls. Shallice (1982), however, has recently reported that this test may not be a reliable indicator of frontal lobe damage. Similarly the two subtests of the two-choice recognition memory test also failed to reveal any specific amnesic deficits in the patients with Parkinson's disease (mean patient scores, words 42.0 (SD 3.1), faces 40.6 (SD 3.6); mean control scores, words 42.2 (SD 3.6), faces 41.2 (SD 3.5)).

On the Word Fluency Test, the patients did significantly worse on the third letter of the test compared with the controls ($U = 317$, $Z = 1.97$, $P = 0.04$) (*see* Table 3).

TABLE 3 RESULTS OF WORD FLUENCY TEST

	Patients' mean (SD)	*Controls' mean (SD)*	*P*
Letter 1 (D)	15.0 (4.7)	16.3 (4.6)	n.s.
Letter 2 (B)	14.0 (5.0)	15.2 (3.6)	n.s.
Letter 3 (M)	12.2 (5.1)	15.2 (4.4)	< 0.05

This was largely due to an increased number of perseverative intrusions occurring in 6 patients and no marked overall reduction in verbal output was found. All 6 patients failed to complete the Wisconsin Card Sorting Test and in 5 the percentage of perseverative errors using Milner's classification was greater than 50 per cent. Three of the same patients also occasionally reverted to words beginning with one of the previous 2 letters. Ten patients compared with 2 controls produced fewer than 10 different words on the third test letter. Eight of these patients had also failed to complete the Wisconsin Card Sorting Test.

DISCUSSION

Stimulation of the caudate nucleus in monkeys is known to disrupt performance on delayed response tests through a mild nonspecific 'arresting' reaction (Akert and Andersson, 1951). What now also seems clear is that the neostriatum of monkeys is not functionally homogeneous and discrete striatal regions appear to process information from localized cortical regions (Rosvold, 1968). For example, Cohen (1972) has demonstrated differential disruptive effects in subregions of the caudate nucleus using a combination of delayed learning and visual discrimination tests. Difficulties in tasks which require response-inhibition are found after lesions of either the orbital frontal cortex or its projection areas in the ventral part of the head of the caudate (Iversen and Mishkin, 1970) and ablation of either the anterodorsal part of the caudate or dorsolateral frontal cortex in subhuman primates cause problems with spatial delayed response tests (Teuber, 1976). On the other hand, the tail of the caudate seems more concerned with visual discrimination and lesions in this site produce deficits which closely resemble those occurring after inferotemporal cortical lesions (Divac *et al.*, 1967). Similar contrasts have been recognized in the putamen, lesions of the ventral areas causing visual programming errors (Buerger *et al.*, 1974), whereas dorsal lesions produce delayed response defects (Teuber and Proctor, 1964). How these cortical and subcortical systems interact with one another is not understood but it seems likely that the corpus striatum is involved in a number of different complex functional acts (Oberg and Divac, 1979). There are considerable problems in assessing the relevance of experimental studies of this sort on animals to normal human behaviour. Nevertheless, some supportive data indicating that the basal ganglia may not just be involved in sensorimotor integration come from the few comparable studies in man. Difficulties with object naming, striking fluctuations of verbal fluency and perseveration occur after left-sided ventral thalamic stimulation. Right-sided stimulation, on the other hand, affects the discrimination and recognition of complex visual patterns (Fedio and Van Buren, 1975; Ojemann, 1975). Bilateral ventral thalamic lesions also cause problems with verbal fluency, perseverations and mild impairment of verbal memory (Ojemann and Ward, 1971).

Proctor and Bowen conducted a series of psychological tests on groups of patients with idiopathic Parkinson's disease. In common with frontal lobe syndromes, parkinsonian patients were found to have abnormalities in setting the visual vertical under conditions of body tilt (the Aubert phenomenon) and difficulties with visual tracking tests which could not be explained totally by eye movement abnormalities or visual field defects (Proctor *et al.*, 1964; Bowen *et al.*, 1972). The patients with Parkinson's disease also displayed errors in setting the visual vertical even in the upright position and made greater misjudgements to the side of their body tilt when asked to assess the postural vertical. The patients with bilateral or left-sided Parkinson's disease did badly on route-walking tests, suggesting that other subtle difficulties in visuospatial orientation were present. Abnormalities of personal space using the verbal portion of the Weinstein body scheme test were also found. Impaired motor performance was not considered an adequate explanation for these disturbances and no direct correlation with motor disability was detected (Bowen, 1976). Other authors have subsequently confirmed perceptual motor disorders in Parkinson's disease. Horne (1971) reported an inability to recognize complex visual stimuli after a brief delay and Danta and Hilton (1975) noted difficulties in tasks depending on judgement of the visual vertical and horizontal which were independent of the severity of bradykinesia. Flowers (1976) was able to demonstrate defective tracking of visual stimuli with a failure to predict movements accurately on spatial tests. Although some of these deficiencies might be attributable to impaired visual memory, much of the data point towards a particular type of perceptual agnosia which is not associated with any higher sensory abnormalities such as astereognosis or visual inattention.

The Wisconsin Card Sorting Test requires a subject repeatedly to change his principal line of reasoning to solve the problems. It has been widely used to investigate inflexibility of abstract thinking in brain-damaged individuals and abnormal responses occur with both anterior and posterior cerebral lesions. Patients with frontal lobe damage have particular difficulties in shifting concepts as a result of continuous perseverative intrusions (Milner, 1964; Drewe, 1974; Nelson, 1976). Many of these subjects give clear verbal indications that they have grasped the conceptual requirements of the task but in some curious way they are quite unable to use this information to guide their actions. Others are aware that they have made errors but seem incapable of correcting them. Milner (1964) therefore suggested that the problems of frontal lobe patients on this test should be regarded as a general inability to change response sets readily in accordance with varying environmental signals rather than as a disorder of abstract thought, and Konow and Pribram (1970) believe that frontal lobe patients have difficulty employing feedback from their own actions which would enable them to modify ongoing behaviour.

Bowen and her colleagues (1975) used the Wisconsin Card Sorting Test to investigate concept formation in 71 unselected patients with Parkinson's disease and 35 controls matched for age and WAIS verbal IQ. All but 18 of the patients were receiving L-DOPA and it is not stated whether the remainder were taking anticholinergic drugs nor how many had received surgery. The patients were found to have considerable difficulty in shifting sets and were frequently unable to attend to the completion of a category. Those receiving L-DOPA produced more correct responses but still could not finish the concepts. Although the total number of errors was significantly increased in the patients, there was no suggestion of increased perseveration.

Our study shows that even in the early stages of Parkinson's disease slight difficulty in completing concepts occurs with an increased percentage of perseverative errors. These findings cannot be attributed to wide differences in overall intellectual function as the two groups were almost perfectly matched on the WAIS verbal and performance scores and on the new adult reading IQ test. Depression, medication and ageing effects were also excluded as relevant factors by the trial design and no memory disturbance could be found on the two-choice recognition memory test. As in Bowen's study, several patients seemed incapable of checking responses they realized to be incorrect, continuing with long runs of perseverative errors. Other individuals discerned the three key categories with little difficulty but were then unable to reduplicate them to complete the whole test. These findings bear a striking resemblance to those reported with frontal lobe damage, although 'frontal lobe signs' such as the grasp and palmomental reflexes reported occasionally in parkinsonian patients were not present. Although it is known that delayed motor response times, as occur in Parkinson's disease, can cause mild impairments in tasks where the patients are under or consider they are under time pressure, this seems an unlikely explanation for the abnormalities observed in the Wisconsin test as patients were informed at the outset and throughout the test that no time strictures were operating.

A reduction in spontaneous speech with an echolalic quality occurs in many patients with frontal lobe damage, and verbal fluency may also be impaired after bilateral thalamic lesions. Patients with left frontal lesions perform particularly poorly on Benton's Word Fluency Test with a reduced verbal output and numerous perseverations. In the present study using this test, difficulty only arose on the third letter and this was due to a reversion by some patients to a previous letter category. Other patients showed an increased number of perseverations and all in all there was no actual reduction in the total number of words given over a minute compared with controls. One patient reiterated the same word four times without realizing his error. We believe that the significant difference between patients and controls on the third letter was due to a difficulty in shifting from one letter category to the next and from one word in the phonetic lexicon to the next. Time pressure may, however, be a contributory factor here. Mayeux and colleagues (1981) have described word production anomia in Parkinson's disease with impairment of category naming, confrontation naming and verbal fluency. They suggest that some of these difficulties might be due to problems in initiating a response set and sequencing and shifting within it. It is also of interest that Bowen (1976) found that difficulties experienced by parkinsonian patients on the route-walking test occurred mainly when the patients were not in the same orientation as the test requirement, suggesting to her that a failure to switch sets competently may have been a contributing factor.

Luria (1965) distinguished two varieties of motor perseveration seen with frontal lobe damage which he believed were caused by involvement of distinct neuronal systems. The first type consisted of compulsive repetition of a movement but the patient could shift fairly easily. This he believed was due to a deep-seated lesion of the premotor zone involving the basal ganglia. The second more severe type additionally involved a difficulty in switching tasks and was thought to be due to massive involvement of the anterior or basomedial portions of the frontal lobe. Luria was convinced that amnesia or lack of understanding could not explain this rigidity and considered a pathological inertia of motor programming to be at fault. Mackie and Beck (1966) also pointed out that perseveration is not invariably associated with intellectual deterioration and Goldstein (1943) has drawn attention to its occasional occurrence as a normal phenomenon when a subject is totally unable to cope with a situation or alternatively when a particular stimulus evokes an excessively strong response. Earlier authors have drawn attention to a bradyphrenia (Naville, 1922) or psychic akinesia (Hassler, 1953) in Parkinson's disease and amongst these anecdotal observations are included allusions to verbal perseverations, word blocks and difficulties attending to the completion of a complicated task.

It is also tempting to speculate that the somewhat inflexible, obsessional personality traits displayed by a number of parkinsonian patients (Pollock and Hornabrook, 1966) might be linked in some way to this difficulty in switching rapidly from one line of thought to another.

Damage to the dopamine-containing mesocorticolimbic pathway is now known to occur in Parkinson's disease (Price *et al.*, 1978; Javoy-Agid *et al.*, 1981). This bundle of cells arising in the ventromedial tegmental area of the midbrain projects to the cingulate, entorhinal and frontal cortex. Its function is not yet known but it may assist the frontal lobe in mediating and monitoring behaviour. The neuropsychological abnormalities observed in this study might be caused by destruction of this pathway, and a comparable loss of dopaminergic neurons in the neighbouring nigrostriatal bundle could explain the reported correlation between motor deficits and intellectual decline reported by others (Mortimer *et al.*, 1982). Some support for this sort of notion comes from the report by Morel-Maroger (1977) of an improvement by L-DOPA of 'frontal lobe signs' in Parkinson's disease.

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ASTEREOGNOSIS AND DISSOCIATED LOSS OF FRONTAL OR PARIETAL COMPONENTS OF SOMATOSENSORY EVOKED POTENTIALS IN HEMISPHERIC LESIONS

DETAILED CORRELATIONS WITH CLINICAL SIGNS AND COMPUTERIZED TOMOGRAPHIC SCANNING

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SUMMARY

Detailed clinical sensory and motor signs were correlated case by case with somatosensory evoked potentials (SEP) in 22 selected patients with a single circumscribed hemisphere lesion. The lesions collectively mapped out a variety of cerebral sites from the anterior frontal to the posterior parietal regions. SEPs were averaged from 8 standard scalp sites with an earlobe reference electrode, so that parietal N20-P27-P45 were differentiated from prerolandic P22-N30 SEP components. SEP wave forms to stimulation on the unaffected side served as the patient's own control.

A complete parietal lesion produced contralateral hemianaesthesia without upper motor neuron signs and eliminated the parietal N20-P27-P45 while the prerolandic P22-N30 persisted at usual latencies. The neural generators for the N20 and the P22 components are thus distinct. It is also proposed that direct, short latency pathways convey somatosensory inputs to the motor cortex, independently of connections *via* parietal areas 2 and 5. Enhancement of P22-N30 after chronic parietal lesions suggests collateral reinnervation by residual inputs after partial deafferentiation of prerolandic cortex.

Small postcentral lesions produced astereognosis (with preserved tactile and deep sensation) and reduced or eliminated the N20 and P27 SEP components, but did not affect the P22-N30 components. Precentral lesions with severe hemiplegia (but not prefrontal lesions) eliminated the prerolandic P22-N30 SEP components and did not alter the parietal N20-P27-P45 components. The data are pertinent to the understanding of the pathophysiology of somatosensory deficits and for the diagnostic use of SEPs in cerebral lesions.

INTRODUCTION

The upper motor neuron signs and somatosensory deficits resulting from cortical lesions in the rolandic region can be dissociated to various extents in patients with more restricted lesions involving appropriate subregions. Sensory deficits of the

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cortical type generally involve spatial and discriminative aspects which are at least in part expressed in the term stereognosis. Loss of this capacity or astereognosis is the failure to identify objects by active palpation, in the absence of visual or auditory information. Astereognosis of the hand opposite to a central lesion implies that the inability to name the object is unrelated to an aphasic or disconnection syndrome. Besides the tactile discrimination of shape and texture, the sense of joint position and movement plays a significant role in object identification since the shape of an object cannot be detected by active touch if the position of the fingers is not perceived. The known superiority of active exploration over passive tactile impression of a pattern must reflect in part the contributon of kinaesthesia (Gibson, 1962). The necessity for integration of several primary somatic inputs for stereognosis was expressed by Denny-Brown *et al.* (1952) when they used the term morphosynthesis.

Impaired recognition of objects can be the result of a loss of the primary somatic sensations in a number of patients with peripheral or central lesions of the afferent pathways. For Dejerine (1914), astereognosis would always be associated with some deficit in the tactile and deep sensations and it was thought to result from deprivation of adequate information through sensory defect (*see* Kennedy, 1924). Wernicke (1895), however, had proposed a different view based on two patients with focal cortical lesions in whom the contralateral astereognosis (*Tastlähmung* or tactile agnosia) occurred in the absence of any significant deficit of primary sensation. Astereognosis without any loss of tactile and deep sensation is usually related to damage to the parietal region (Guillain and Bize, 1932; Lange, 1936; Critchley, 1953; Denny-Brown *et al.*, 1952), but the extent and location of the critical cortical areas involved is still far from clear. Because stereognosis implies higher order integration, the associative cortex of the superior parietal lobule has been implicated (Evans, 1936; Semmes *et al.*, 1954; Nielsen, 1962). Evidence has also been presented that lesions of the postcentral gyrus may be necessary to produce astereognosis (Corkin *et al.*, 1970; Roland, 1976).

These and other issues about the functional organization of cortical areas subserving specific somatosensory functions in man can be addressed anew by combining detailed clinical studies of patients with the analysis of scalp-recorded averaged somatosensory evoked potentials (SEP). The SEPs to electrical stimulation of fingers or median nerve on one side consistently present characteristic component potentials that reflect the serial activation of distinct neural generators by the afferent volley. SEP components are conveniently labelled from their polarity (N for negative, P for positive) and modal peak latency in normal subjects of standard body size (*see* Donchin *et al.*, 1977). The standard SEP components recorded from the scalp with a noncephalic reference electrode include the short latency positive far field P9-P11-P14 potentials that reflect the volume conducted input volley ascending from brachial plexus (P9) through the dorsal columns (P11) and medial lemniscus (P14); these far field potentials are followed by a widespread N18 and by the cortical SEP components (*see* Cracco and Cracco, 1976;

Kritchevsky and Wiederholt, 1978; Kimura *et al.*, 1978; Chiappa *et al.*, 1980; Wiederholt, 1980; Desmedt and Cheron, 1980*a*, *b*, 1981*a*, *b*; Anziska and Cracco, 1980; Mauguière and Courjon, 1981).

Many previous SEP studies involved recording montages in which a frontal scalp electrode served as reference (connected to grid 2 of the amplifiers) while the active electrodes over the parietal scalp were connected to grid 1 of the amplifier. Under these conditions, the cerebral potentials picked up over the front are algebraically subtracted from the parietal scalp potentials, while the far field potentials with widespread scalp distribution tend to cancel out (*see* Desmedt and Cheron, 1980*a*, 1981*b*, 1982). Such recording conditions are not acceptable if the aim of the study is to identify any specific alterations of SEP components that may result from focal cortical lesions. For example, if a set of postcentral SEP components recorded *via* grid 1 of an amplifier was genuinely eliminated or enhanced as a result of a given cortical lesion, this change would easily either be overlooked or misinterpreted in the (parietal to front) recorded trace since the latter would include any concomitant potential recorded *via* grid 2 of the same amplifier by the 'reference' electrode placed on the front. Much of the current confusion in the SEP discussions can be traced to the unfortunate use of such electrode montages. The difficulties can be avoided by using a noncephalic electrode as reference whereby the actual SEP components picked up at any scalp site are genuinely displayed in the trace (Desmedt and Cheron, 1982). In noncephalic reference montages, the two electrodes are further apart and this can make the recording more vulnerable to interference from ECG or unwanted muscle potentials when conditions are suboptimal in certain patients. As a compromise, we used recording montages with an earlobe reference electrode which is less susceptible to such interference, but allows adequate differentiation of the genuinely distinct potentials which have been shown to be generated either in front or behind the rolandic fissure (Desmedt and Cheron, 1981*b*). The N20-P27-P45 SEP components recorded over the parietal scalp (contralateral to the hand stimulated) are to be distinguished from the P22-N30 SEP components simultaneously recorded over the prerolandic scalp and they show different onset and peak latencies as well as independent changes in the course of ageing (Desmedt and Cheron, 1980*b*, 1981*b*). In normals, the frontal N30 SEP component is usually bilateral (fig. 1, B7, B8)), while the contralateral parietal N20 is not present ipsilaterally (Desmedt and Robertson, 1977; Desmedt and Cheron, 1981*b*).

The present study examines how distinct clinical (motor and/or sensory) deficits correlate with specific changes of the different cortical SEP components in selected patients with a clearly defined, single uncomplicated hemisphere lesion. The changes of either the parietal or the prerolandic SEP components were separated and correlated case by case with the pattern of clinical signs. The results provide new evidence on the pathophysiology of astereognosis. They also substantiate the view that the parietal or prerolandic SEP components in man have separate neural generators and must involve distinct anatomical pathways from thalamus.

MATERIAL AND METHODS

Twenty-two patients (11 males) with single circumscribed hemisphere lesions outside the basal ganglia were selected from a much larger group. The median age was 53 years. The youngest patient was 10 and the oldest 75 years. Four were older than 65 years. All were right-handed by the Edinburgh inventory criteria (Oldfield, 1971).

Unambiguous evidence for location and extent of the lesion was secured in each patient. CT scans were available for all patients except cases 8 and 12. They were taken in the usual oblique plane at 15 to 20 deg to the canthomeatal line, with slices of 10 mm thickness. Pixel (picture elements) was 1 × 1 mm The figures present for each patient accurate drawings of all the CT scan sections that included the lesion, thereby providing a fair display of the true three dimensional extent of the lesion. Carotid angiography was performed in 7 patients and a radionuclide scan in one. There were 8 ischaemic lesions or cerebral infarcts, 6 intracerebral haemorrhages, 2 angiomas, 1 prefrontal leucotomy, 1 head injury and 4 tumours. None of the patients had a history of epilepsy, cerebrovascular accident or cranial trauma prior to the present illness. Patients with diffuse cortical atrophy, marked enlargement of the cerebral ventricles or systemic disease were also excluded.

On the day of SEP study, a repeat clinical examination documented in detail the motor and sensory deficits. The following features were tested in each patient. (1) Tactile sensitivity for smooth objects or cotton mesh, and to nonpainful pinprick; the latter were repeated at easy intervals to check for any progressive hyperpathic reaction. (2) Pain and temperature sensation. (3) Two-point discrimination on the finger tip, palm and dorsum of either hand. (4) Vibration sense at knuckles, wrists, iliac crests and malleoli. (5) Joint position sense, tested by the ability of the patient to identify flexion or extension of fingers or toes with closed eyes, to reproduce passive finger movements with the control limb, and to mimic with the affected hand any position imposed on the control finger. (6) Graphaesthesia, assessed by the recognition of capital letters or figures drawn with a smooth object on the palm or dorsum of each hand, and on the dorsal aspect of each forearm. (7) Stereognosis, tested by the recognition of familiar objects by palpation with eyes closed; aphasic patients answered by pointing to the palpated object exposed among others on a table. (8) Unilateral tactile extinction to bilateral simultaneous stimulation with smooth contact (or with nonpainful pinprick in cases with tactile loss) on symmetrical fingers or on the dorsum of both hands. (9) Constructional apraxia, assessed by the ability to draw familiar objects (bicycle, cube, flower or house) on paper, with or without a model. (10) Ideomotor apraxia, tested by mimicking symbolic gestures (military salute, sign of the cross) or implement manipulation (hammer, screwdriver, corkscrew).

For SEP recording, the subject lay supine on a couch in a warm, quiet, semidarkened room. He was relaxed with closed eyes. The stimuli were 0.2 ms square wave electrical pulses delivered either to the median nerve at wrist (cathode proximal; intensity just above thumb twitch threshold), or to fingers II and III (usually 3 times subjective threshold). Several runs of 500 or 1000 trials each were performed by stimulating successively either the left or the right side. The intervals between stimuli varied at random between 500 and 600 ms. The SEPs were recorded with 8 electrodes placed on each side of the head at parietal, central and frontal sites (*see* figurines in each figure). The parietal electrodes were located 3 cm behind the vertex Cz and at 7 cm from the midline. The prerolandic electrodes were placed 2 cm in front of the vertex Cz and at 5 cm from the midline. The standard frontal electrodes were at 7 cm in front of Cz and at 6 cm from the midline. In certain patients, additional anterior frontal or posterior parietal sites were recorded to document further the scalp extension of some components or to check for an apparent absence or abnormality of some SEP components (*see* figs.). The earlobe of the same side served as reference. The EEG was monitored throughout the recording session. All channels were simultaneously averaged, each with 512 or 1024 points of 136 μs bin width. The overall bandpass extended from 1 to 3000 Hz. Samples with excessive EMG interference were automatically rejected (*see* Desmedt, 1977, for details of the techniques).

The averaged SEPs recorded over the affected and control hemispheres were illustrated as unsmoothed traces drawn by the computer, with negativity of the active scalp electrode producing an upward movement of the trace. Records to either right or left stimulation were compared to facilitate assessment of abnormal components. Thus each subject was used as his or her own control. This was important to validate changes of SEP components due to the unilateral lesion since it is now well known that SEP wave forms present a wider range of intersubject variations than previously recognized (*see* Desmedt and Cheron, 1980*b*, 1981*b*). Highly consistent waveforms were obtained in repeat runs on the same patient, but these were usually not illustrated to avoid overloading the figures.

RESULTS

Unilateral Prefrontal Lesions

The 5 patients of this subgroup had a lesion rostral to the frontal horn of the lateral ventricle and to premotor area 6. All patients gave normal results in all the tests of somatic sensation described in Methods. The clinical signs in this subgroup were characteristic of the frontal syndrome, and included emotional indifference, reduced spontaneous speech (smiling mutism in Case 4), slowing of intellect, reduced initiative and slight hypokinesia (but with no extrapyramidal signs).

Case 1, a female aged 18 years, developed over six months adversive seizures to the right with vocalization and secondary generalization. Nine days after a fairly extensive left frontal lobectomy documented by CT scan (fig. 1A), the patient had recovered well and normal SEPs were recorded for stimulation of the right (fig. 1B) or left (fig. 1C) median nerve: the widespread far field P14 was followed by standard contralateral parietal N20-P27-P45 components, and by prerolandic P22-N30 potentials. The latter were recorded at central, frontal and even anterior frontal sites bilaterally (cf. electrodes 7 and 8). The lack of anomaly of size or latency of the P22-N30 SEP components suggested that they must be generated more posteriorly than at the prefrontal region. In contrast, the EEG showed left frontal slowing at 3 to 4 Hz and isolated spike-wave complexes.

Prerolandic P22-N30 components were also present in the 4 other patients with prefrontal lesions. Case 2, a female aged 63 years, developed over two years progressive behavioural indifference and then presented an episode of temporospatial disorientation with formed visual hallucinations. The CT scan showed a large parasagittal meningioma extending vertically from the ethmoid ridge to the upper third of the frontal lobe (fig. 2A). The SEPs recorded before operation, at the time of the CT scan examination, were normal, as was the EEG. Cases 3, 4 and 5 had presented one to three years before the SEP study with an intracerebral haemorrhage located dorsolaterally in the right frontal lobe (fig. 2B) or medially in the left frontal lobe (fig. 2C, D). These CT scans document the lesion size shortly after the vascular accident, whereas the SEP study was performed several months later when the lesion had stabilized. The SEPs were similar to controls, except in Case 5 in whom N30 was significantly enhanced in voltage on the side of the lesion. The EEG showed intermittent frontal slowing to 4 to 7 Hz on the side of the lesion in all patients.

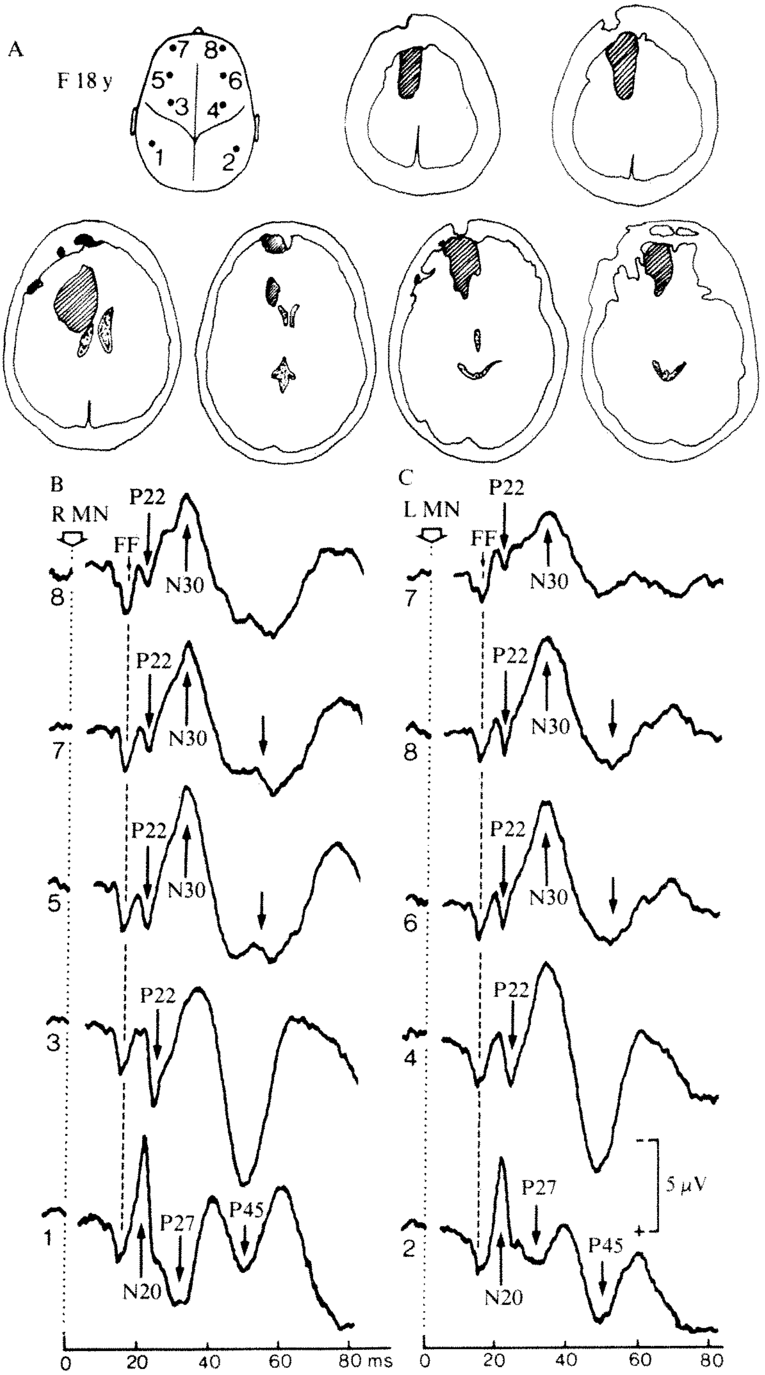

FIG. 1. *Case 1*, female aged 18 years, nine days after left prefrontal lobectomy. A, figurine with recording electrodes sites (earlobe reference) and the CT scan sections that included the lesion (right hemisphere presented on the right side of all drawings). B, SEPs to right median nerve (MN) stimulation. C, SEPs to left median nerve stimulation. The numbers before each averaged trace refer to the corresponding scalp site of the electrode on the figurine. The vertical interrupted line identifies the widespread far field P14 (FF).

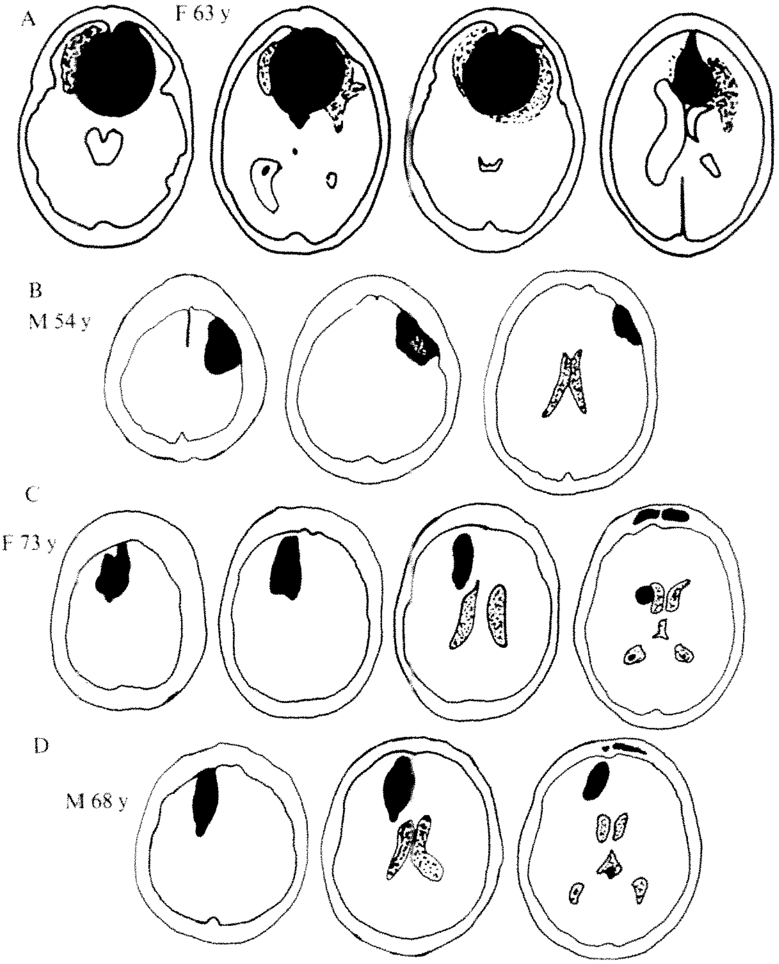

FIG. 2. Drawings of CT scan sections depicting the prefrontal lesions in Cases 2 (A), 3(B), 4(C) and 5 (D). *See text.*

Thus the patients of this subgroup had no somatosensory deficit and preserved prerolandic P22-N30 SEP components. The extensive recent and well-delineated surgical lesion in Case 1 is particularly conclusive.

Unilateral Precentral Lesions

The 4 patients of this subgroup displayed clear abnormalities in the prerolandic SEP components (Table 1). Case 6, a male aged 59 years, developed in 1976 partial Bravais-Jacksonian epilepsy with clonic seizures of left foot or hand, sometimes extending to the left half of the body but sparing the face. The CT scan showed a right rolandic-parietal mass (fig. 3A) which proved to be a grade I astrocytoma when removed surgically in May, 1981. Seven days later, the patient presented with a

TABLE 1. CORRELATIONS BETWEEN CLINICAL SIGNS AND LOSS OF DIFFERENT 'SEP' COMPONENTS IN PATIENTS WITH FOCAL UNILATERAL CNS LESIONS

Stereognosis	*Position*	*Tact*	*Upper motor neuron*	*Far field P14*	*P22-N30*	*N20*	*P27-P45*	*Case No.*	*Lesion site*
0	0	0	0	+ +	0	0	0	21	Capsulothalamic
0	0	0	0	+ +	0	0	0	19, 20	Pre- and postcentral cortical lesion
0	0	0	+ +	+ +	+ +	0	0	10, 14	Complete parietal cortical lesion
0	0	+ +	+ +	+ +	+ +	0	0	11	Parietal cortical lesion
0	+ +	+ +	+ +	+ +	+ +	+	+	12, (15), (17), 18	
+ +	+ +	+ +	0	+ +	0	+ +	+ +	6, 7	Precentral cortical lesion

For patients (15) and (17) the prerolandic SEP was not recorded. 0 = loss of function (or component), + + = normal, + = reduced or altered. An example of patient with all columns at '0' (with loss of far field P14) after high cervical spinal cord lesion is described by Mauguière and Courjon, 1981.

The Table does not include the patients with a prefrontal lesion (Cases 1 to 5) or the few cases in whom stereognosis could not be tested (Case 9) or in which the lesion was extensive (Case 22).

complete flaccid hemiplegia involving the left hemiface, arm and leg: this suggested a large precentral lesion. However, tactile (two-point discrimination), and pain, temperature, and vibration sense were preserved. Position sense was slightly impaired in the fingers on the left. Stereognosis tests were performed more slowly by the left hand, but the answers were correct. It was uncertain whether this slowing without any actual error was related to the clinically evident central paresis of the left hand or to some surgical damage to the parietal region during removal of the large tumour, or both. There was also extinction on the left on bilateral stimulation of the hands and feet. The CT scan was performed at the time of the SEP study (fig. 3A). The control SEPs on stimulation of the median nerve (fig. 3B) or fingers (E) on the normal side presented all the usual components after the widespread far field P14. However, stimulation of the left median nerve (C) or fingers (F) on the affected side elicited no perolandic P22 or N30 component either contralaterally (fig. 3, C6, F6) or ipsilaterally (C5). The parietal N20 had normal size and latency (fig. 3, C4, C2, F4), but increased duration, and the subsequent parietal positivity was reduced on the side of the lesion. The EEG showed only occasional right parietocentral slowing at 3 to 4 Hz.

SEPs were again recorded when this patient had improved, four months after operation. He then presented a much less severe spastic hemiplegia, more severe in the upper limb. He was able to walk with a stick or to drink from a glass with his left hand. Stereognosis, position sense, two-point discrimination and graphaesthesia were normal on the left. The left tactile extinction on bilateral stimulation was still present. In the SEP with stimulation on the affected side, the parietal N20 was still delayed and the frontal N30 remained virtually absent, but a small P22 could now be identified.

Case 7, a girl aged 10 years, suddenly developed an upper motor neuron disorder with Broca's motor aphasia, but no detectable sensory loss, from an intracerebral haemorrhage in the left prerolandic region. Carotid angiography showed a localized arteriovenous malformation and surgery was performed. When SEPs were studied

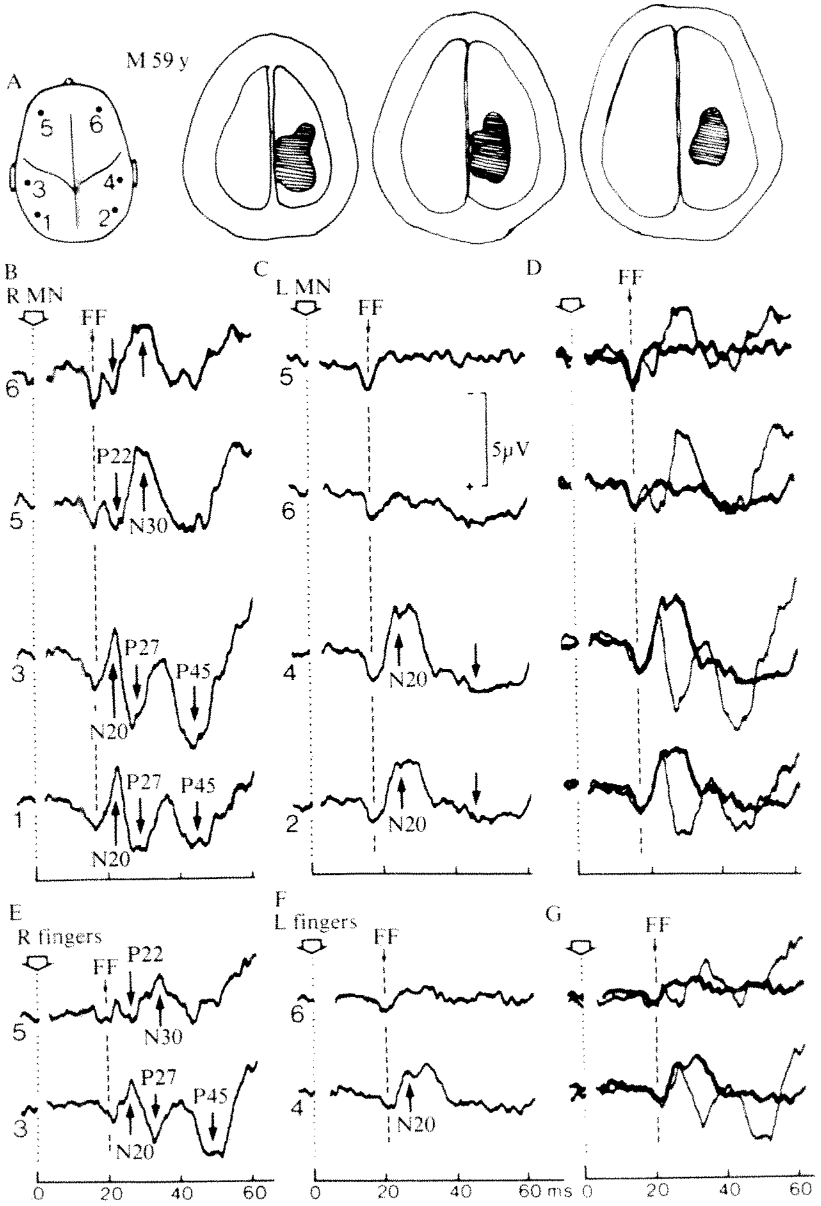

FIG. 3. *Case 6*, male aged 59 years, with hemiplegia and massive cortical and subcortical precentral lesion. Same presentation of the data. Electrical stimulation of the median nerve (B, C) or of fingers II-III (E, F) either on the affected side (C, F) or on the normal side (B, E). D and G show the same superimposed SEPs, the thicker trace corresponding to stimulation on the affected side.

one year later, the patient still had a severe right spastic hemiplegia and a left rolandic lesion in a CT scan (fig. 4A). A moderate dysphasia with dysarthria persisted, but did not interfere with sensory testing which disclosed normal stereognosis and somatic sensation in the right arm. The parietal N20-P27-P45 complex was present with stimulation on either side, but with a somewhat smaller voltage on the affected side (fig. 4B1). However, the prerolandic P22 and N30 were absent on the side of the lesion (B3). The EEG showed intermittent left frontal and anterior temporal slowing at 4 Hz.

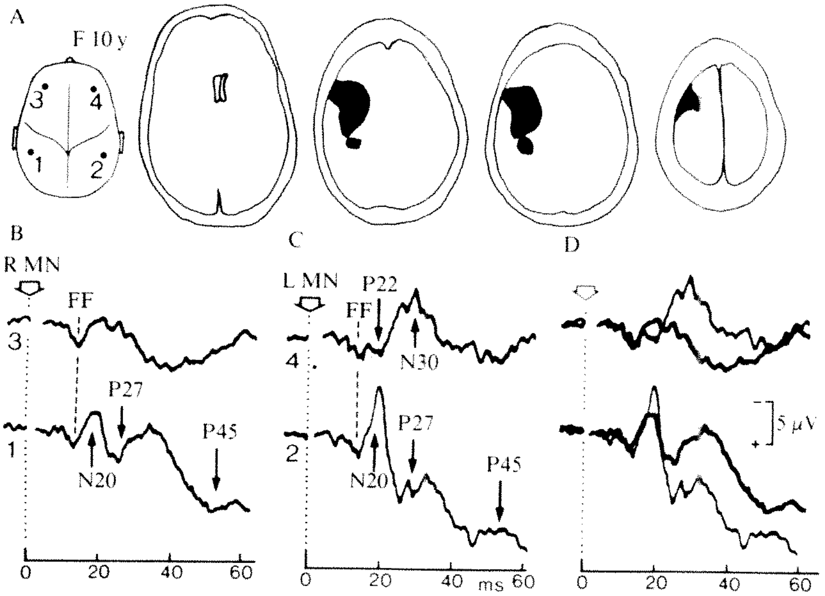

FIG. 4. *Case 7*, female aged 10 years, one year after operation for intracerebral haemorrhage. Stimulation of the median nerve on the affected (B) and on the normal (C) side. Superimposed traces shown in D, as in fig. 3.

Case 8, a female aged 23 years, had a history of recurrent transient ischaemic attacks with hemiparesis and tingling paraesthesiae on the left side since the age of 12 years. A CT scan was not performed, but right carotid angiography showed a large precentral arteriovenous malformation (fig. 5A). At the time of the SEP study one week later, upper motor neuron signs were absent, while sterognosis and somatic sensations were normal. The parietal N20 and P27 were present, but with slightly different profiles with stimulation on either side (fig. 5, B1, C2). No useful statement can be made about possible changes of the preroland P22 component (C4) since the control P22 in the SEP to stimulation on the normal side was poorly delineated in this patient (B3). However, the frontal N30 was clearly reduced on the side of the lesion, where the upward (negative) displacement of the trace (arrow in C4) is probably to be interpreted as a widespread N18 potential which recent evidence shows to be generated subcortically (Mauguière *et al.*, 1983). The SEP

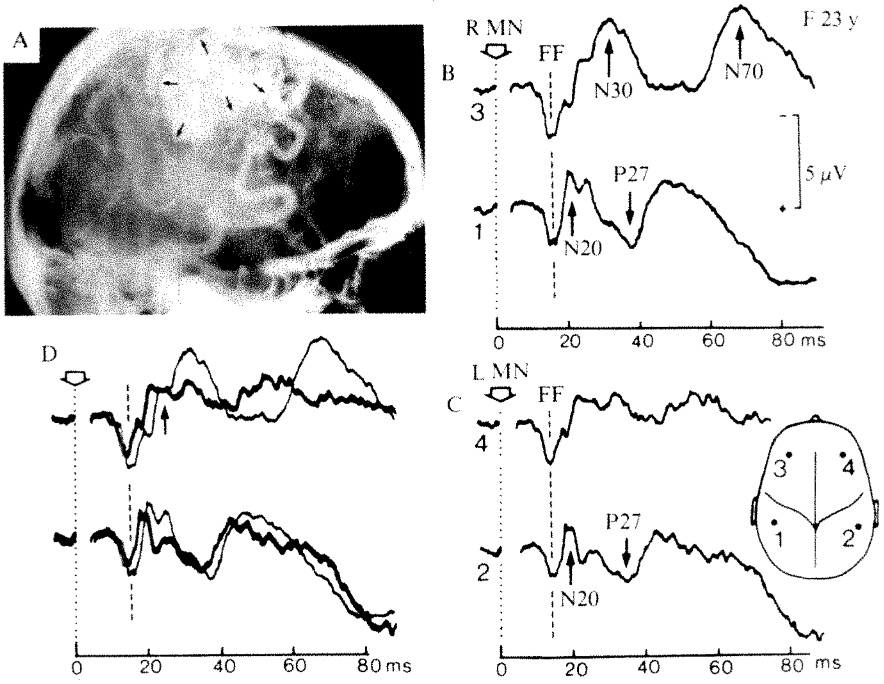

FIG. 5. *Case 8*, female aged 23 years, with a precentral arteriovenous malformation shown by carotid angiography (A). Stimulation of the median nerve on the normal B and C on the affected side. D, Superimposition of the same traces to compare SEPs to stimulation on the affected side (thicker traces) with SEPs to stimulation on the normal side at the frontal (above) and parietal (below) recording sites.

traces from either side were superimposed in D in order to demonstrate better the virtual lack of a well-delineated precentral N30 on the side of the lesion. The patient unfortunately did not survive operation which confirmed an extensive vascular lesion in the precentral region.

Case 9, a male aged 63 years, presented with a sudden left hemiplegia due to occlusion of the right internal carotid artery (arteriography). The CT scan showed a right frontal low density lesion (fig. 6A). At the SEP study three weeks later, there was a left Babinski sign with a complete flaccid hemiplegia, but no asomatognosia. Tactile and position sense were preserved in the left hand. Severe central paralysis on the left side prevented testing for stereognosis. Left-sided extinction was observed for bilateral tactile, auditory and visual stimulation. On stimulation of the fingers on the affected side, the parietal N20 (fig. 6C2) was similar to control (B1) while the P27 and P45 presented a similar profile but with a somewhat larger amplitude. At the prerolandic site, the control hemisphere (B3) presented a normal pattern with a P22 and an N30. On the other side (C4), P22 and N30 seemed to be missing and a 'postcentral pattern' appeared instead with a slightly attenuated N20 but quite large P27 and P45. At the more anterior frontal site (C6) the far field P14 appeared to be

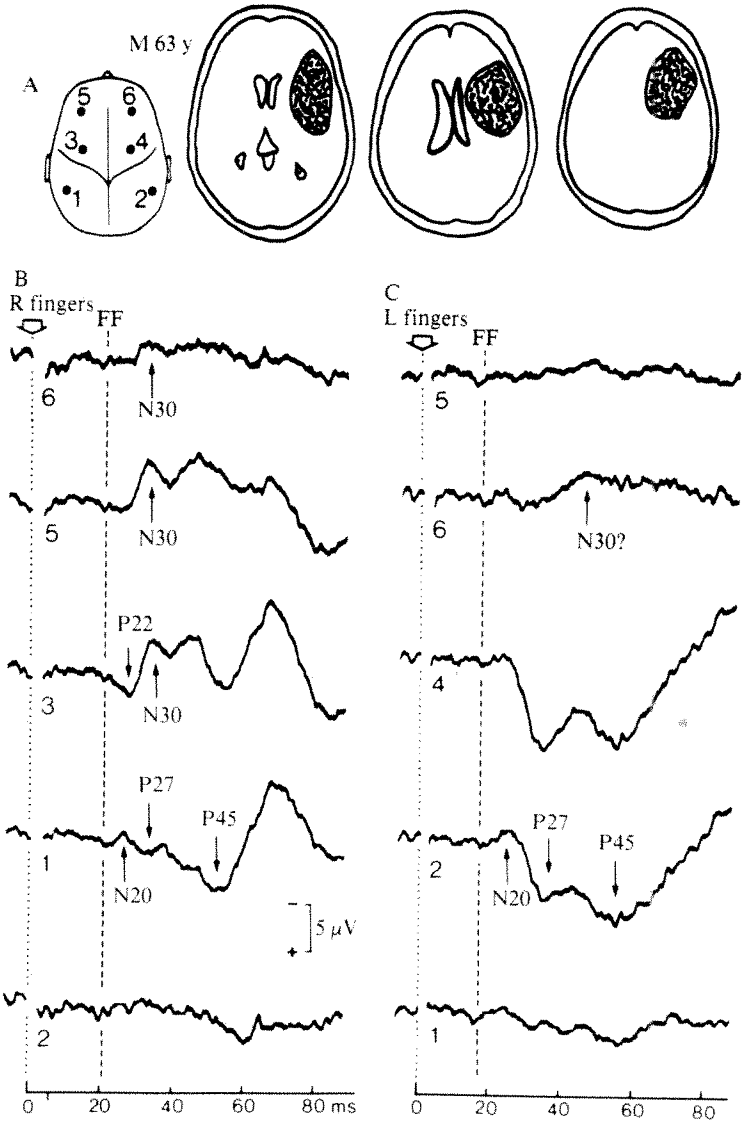

FIG. 6. *Case 9*, male aged 63 years, three weeks after occlusion of the right internal carotid artery. Electrical stimulation of fingers II-III on the affected side elicits doubtful frontal N30 (C6) and no P22. The precentral trace shows normal parietal components that are conducted forwards by volume conduction on the scalp (C4). Parietal components are present contralateral to the stimulus (B1, C2), and absent ipsilaterally (B2, C1). The far field P14 (vertical interrupted line) is rather small and ill-defined in this patient.

followed only by a small and delayed negativity which may or may not represent a true N30. In any case, the contrast with the symmetrical control side (B5) is striking. At the ipsilateral anterior frontal site (C5) no SEP component can be identified.

The possibility of picking up sizeable parietal SEP components at a scalp electrode placed in front of the rolandic sulcus has been documented for senile SEPs, in conjunction with the presence of rather small frontal components (Desmedt and Cheron, 1980*b*, fig. 6D; 1981*b*). The parietal positivities indeed appear to be generated rather close to the rolandic sulcus and they can apparently be volume-conducted rather efficiently towards the prerolandic electrode when N30 is reduced, as is the case of this patient. The EEG showed slow bursts at 4 Hz at the right frontal leads.

Thus the prerolandic P22-N30 SEP components were reduced or abolished in this subgroup, in conjunction with a precentral lesion and upper motor neuron signs, but in the absence of clear somatosensory deficit (Table 1).

Unilateral Parietal Lesions

Opposite dissociations between pre- and postrolandic SEP components were found in this subgroup of 7 patients (Table 1). Case 10, a female aged 53 years, suddenly developed a right hemianaesthesia and hemianopia, with bilateral apraxia and severe Wernicke's aphasia with agraphia, due to a left middle cerebral artery embolism in the course of carotid surgery. Five years later, a severe right hemianaesthesia was still present with complete astereognosis and loss of tactile, pain, temperature, vibration and joint position sense. The remarkably clear cut postcentral location of this lesion was evidenced clinically by the absence of a Babinski sign and of a central motor deficit, and by normal tendon reflexes. Several CT scans at yearly intervals showed a consistent and stable parietal lesion (fig. 7A). With finger stimulation on the affected side, the contralateral SEP showed a giant prerolandic P22 followed by large negative components (fig. 7, B3, B5) which also appeared ipsilaterally (B6). These prerolandic SEP components were unexpectedly picked up with identical latencies, but smaller size, at the postcentral electrode (B1) where no N20 was identified. The maximum amplitude of the P22 and N30 occurred at the prerolandic site (B3). For these SEP components to be correctly interpreted, it should be mentioned that the peak latency of the N22 (actually 26 ms) corresponds to that of the P22 recorded on the control side (C4) and is in line with the latencies for stimulation of fingers which are longer than for stimulation of the median nerve. Actually the superimposition of the traces recorded from symmetrical scalp sites in D shows clearly that the P22 presents an identical onset latency for stimulation of either the lesion or the control sides (*see* second and third frames in D). We interpret the early positivity recorded at the left parietal site (C1) as a P22 conducted backwards by volume conduction because this component has an onset latency that is clearly shorter than that of the parietal P27 recorded on the control side (C2), as better demonstrated in the fourth frame of superimposed traces in D.

The remarkable finding of an absent early parietal response in conjunction with enhanced prerolandic P22-N30 potentials was validated in other runs with electrical stimulation of the same fingers at lower intensity (that is, near the threshold for subjective sensation on the normal side). This control was important to document the consistency of the finding irrespective of the chosen intensity of the evoking stimulus. For this near-threshold stimulation, the P22 was somewhat smaller precentrally (E3) and it no longer diffused backwards to the parietal site (E1) where the SEP trace only showed residual noise without identifiable parietal N20-P27 SEP components. These data provide strong evidence that large P22-N30 prerolandic

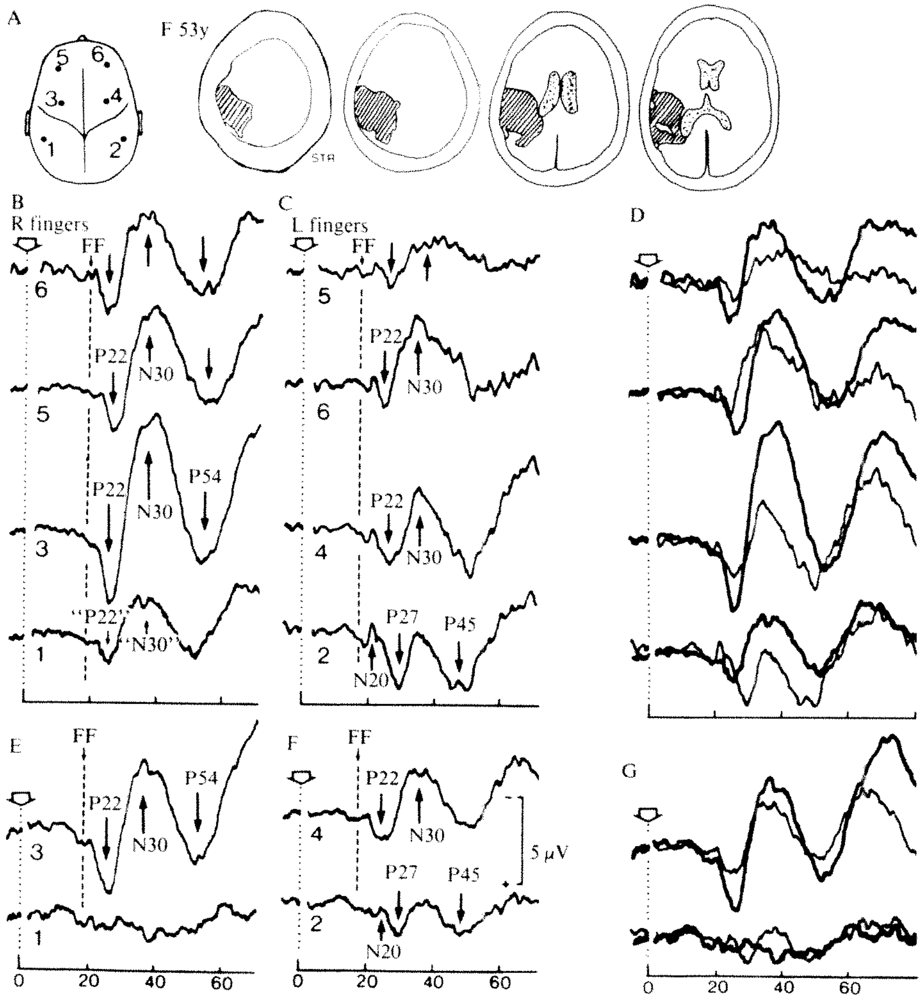

FIG. 7. *Case 10*, female aged 53 years, with a complete lesion of the left parietal region since the age of 5 years and a complete contralateral hemianaesthesia. Electrical stimulation of fingers II-III at intensities three times threshold (B, C) or near threshold (D, E) of the normal side. Notice the conduction backwards by volume conduction of the enhanced prerolandic P22-N30 to the parietal scalp recording site (B1). The same records are superimposed in D and G, with the thicker trace corresponding to the SEPs to stimulation on the affected side.

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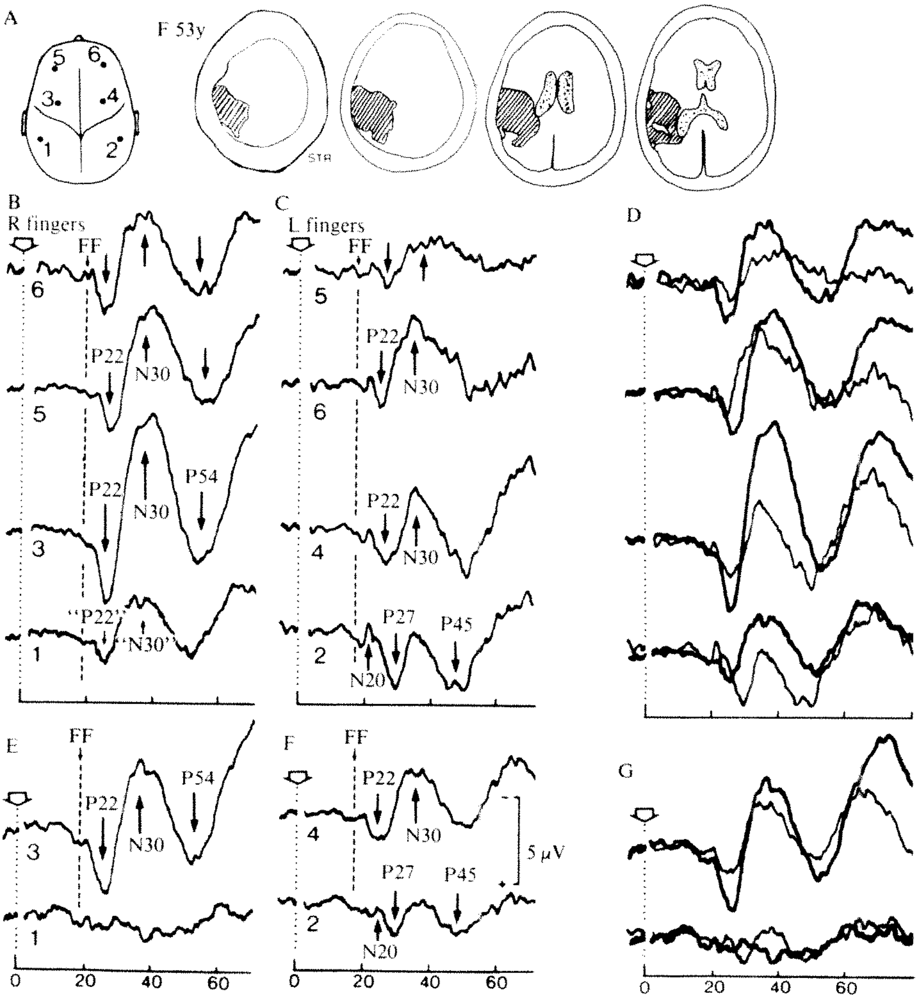

FIG. 7. *Case 10*, female aged 53 years, with a complete lesion of the left parietal region since the age of 5 years and a complete contralateral hemianaesthesia. Electrical stimulation of fingers II-III at intensities three times threshold (B, C) or near threshold (D, E) of the normal side. Notice the conduction backwards by volume conduction of the enhanced prerolandic P22-N30 to the parietal scalp recording site (B1). The same records are superimposed in D and G, with the thicker trace corresponding to the SEPs to stimulation on the affected side.

recording six months later. The patient had complete astereognosis, impaired joint position sense, absent graphaesthesia and tactile extinction in the right hand. Tactile, pain, temperature and vibration sense were present. There was no Babinski sign or any upper motor neuron deficit. Left finger stimulation elicited a normal N20 parietal response (fig. 8C2), followed by only one clear positive peak P40 instead of the more common 'W' pattern with the P27-P45 (*see* Desmedt and Cheron, 1981*b*). The prerolandic P22 was barely identifiable (C6) and the N30 unusually small for a patient of only 44 years. An N30 nevertheless appeared on the ipsilateral side (C5). A later frontal negativity N56 was recorded. These features can be considered within the range of normal control SEPs in the series studied in Lyons and in Brussels. They emphasize that interpretations of SEPs in patients with unilateral lesion should indeed rely on the comparison with the normal side in the same individual. Right finger stimulation on the affected side elicited no parietal N20 or any early positivity (B1). However, the prerolandic P22 could be more reliably identified on this side (B3, B5) and it was followed by a rather large N30 that also occurred ipsilaterally (B6). Other runs with stronger median nerve stimulation on the affected side (not illustrated) only evoked a miniscule parietal N20 that was much smaller than control, the parietal positivity remaining absent. The EEG showed intermittent bursts of slowing at 3 to 4 Hz over the left temporoparietal region.

Case 12, a female aged 75 years, developed clumsiness of the left hand without weakness in March, 1979 ('main instable ataxique' of Alajouanine *et al.*, 1934). A radionuclide scan disclosed a right posterior parietal infarct with increased uptake (fig. 9A). No CT scan was undertaken. At the time of the SEP study three months later, the left hand showed complete astereognosis, tactile extinction and loss of graphaesthesia. Tactile, pain, temperature, vibration and joint position sense were preserved. There was a Babinski sign and rather brisk tendon reflexes on the left, but no detectable weakness. Stimulation of the fingers on the left elicited SEPs with a relatively normal parietal N20 and P27 components at this three time threshold intensity (fig. 9B2). In fact these parietal responses cannot be considered as significantly different from those on the control side (C1) as further shown in superimposed traces (third frame in D). The prerolandic P22 and N30 were again markedly enhanced (B4) and offered a sharp contrast to the control responses for stimulation on the normal side (C3). The P22 and N30 responses in the latter can be considered within the normal range in view of the age of this patient (75 years). It has been recently shown that the frontal N30 tends to be reduced in ageing human subjects (Desmedt and Cheron, 1981*b*, Table 1). The superimposed traces indicate that these components were markedly enhanced on the affected side, without significant changes in their latencies (second frame in D). The study of ipsilateral frontal responses further indicates that none was present for stimulation on the control side (C4), in keeping with the patient's age, while a large N30 was recorded for stimulation on the affected side (B3). This indirectly substantiates the interpretation of an abnormal potentiation of the prerolandic responses on the side of the lesion. Repeat tests with near-threshold stimuli delivered to the same fingers

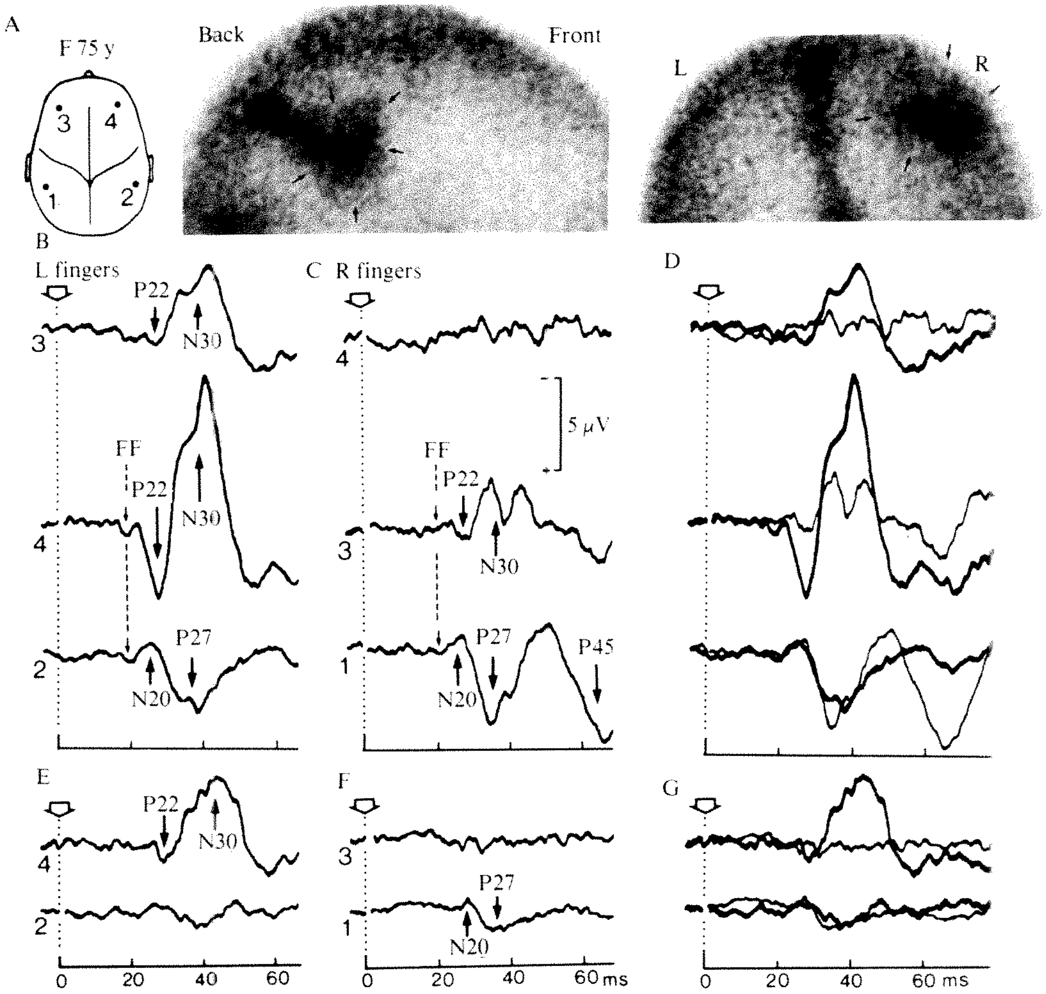

FIG. 9. *Case 12*, female aged 75 years, three months after a right posterior parietal infarct shown in the radionuclide scan (A). Electrical stimulation of fingers II-III at usual (B, C) or lower near-threshold (D, E) intensities. Note the absence of parietal N20-P27 in E2. The frontal negativity on the normal side is small (C3), and virtually absent for near-threshold stimulation (F3) in this old patient. The same records are superimposed in D and G, with the thicker trace corresponding to the SEPs to stimulation on the affected side.

disclosed an even greater contrast: the parietal SEP components were virtually absent on the affected side (fig. 9, E2) but present on the control side (F1), while the prerolandic P22-N30 were still quite large on the affected side (E4) but absent in the control trace (F3). These findings are in line with the hypothesis of an abnormal cerebral hyperreactivity that reflects plastic changes following chronic loss of neural connections normally received from another brain region that has been destroyed by a focal lesion (*see* Discussion). The EEG was normal in Case 12.

Case 13, a female aged 67 years, developed partial motor seizures affecting the left side. She was not aphasic, had no abnormal motor signs and the plantar responses were flexor. Tactile, temperature, and pain sensation was intact. A severe ideomotor apraxia was evident for the left hand, with complete inability to name palpated objects even though correct tactovisual matching was possible with this hand (*main gauche anomique* of Schott *et al.*, 1969, or 'tactile aphasia' of Geschwind and Kaplan, 1962). There was complete astereognosis in the right hand and some apraxia for bimanual activities. There was no left hemianopia. At the time of the SEP study, the CT scan showed a large bilobed tumour invading the splenium of corpus callosum, the left parietal white matter and the left posterior parietal cortex (fig. 10A). The frontal SEPs to median nerve stimulation on either side had similarly delayed negativities (fig. 10, B5, C4) which may have been related to brain distortion by the large tumour. The parietal SEP to right median nerve stimulation showed a large N20 followed by reduced and delayed positivity (B1).

When using finger stimulation that produced a smaller input volley, the alterations in the response from that side were more clearly revealed, with a much delayed parietal N20 (peak at 31 ms, D1) and an absence of parietal positivities P27-P45. This absence of positive components on the affected side is significant in view of the large P27 and P45 components recorded on the control side (E2). The N30 was virtually absent (D5), although this patient was only 67 years old, but a clearly delineated prerolandic P22 was recorded (D3, D5). The EEG showed rather frequent asynchronous bursts of slowing at 3 to 4 Hz which predominated over the frontoparietal regions of both hemispheres. Thus this patient featured preserved SEPs on the side exhibiting tactile anomia, but distorted or absent parietal positivities (and a preserved prerolandic P22) on the other side where there was complete astereognosis.

Case 14, a male aged 47 years, presented in 1976 with a sudden cerebral vascular lesion that gave rise to left hemianaesthesia and a left upper quadrantanopia which were still present at the time of the SEP study in 1981. The CT scan then showed an area of reduced density in the right parieto-occipital and posterior thalamic regions (fig. 11A). There was complete astereognosis in the left hand, with loss of position sense and of graphaesthesia, and considerably reduced tactile sensation (absent two-point discrimination). There was no tactile extinction. Pain, temperature and vibration sense were preserved. Exposure of the left hand to heat or cold was described as unpleasant. The tendon reflexes were brisk on the left, but the plantar responses were flexor. Left fingers showed a slight motor deficit only for skilled movements. Electrical stimulation of the left median nerve on the affected side elicited fairly normal prerolandic P22-N30 SEP components (fig. 11C4), but virtually no parietal SEP components after the far field P14 (C2). Stimulation on the normal side evoked well-delineated parietal N20 and P45 (B1), as well as prerolandic P22-N30 components serving as control. The EEG showed intermittent right parietal slowing at 4 Hz.

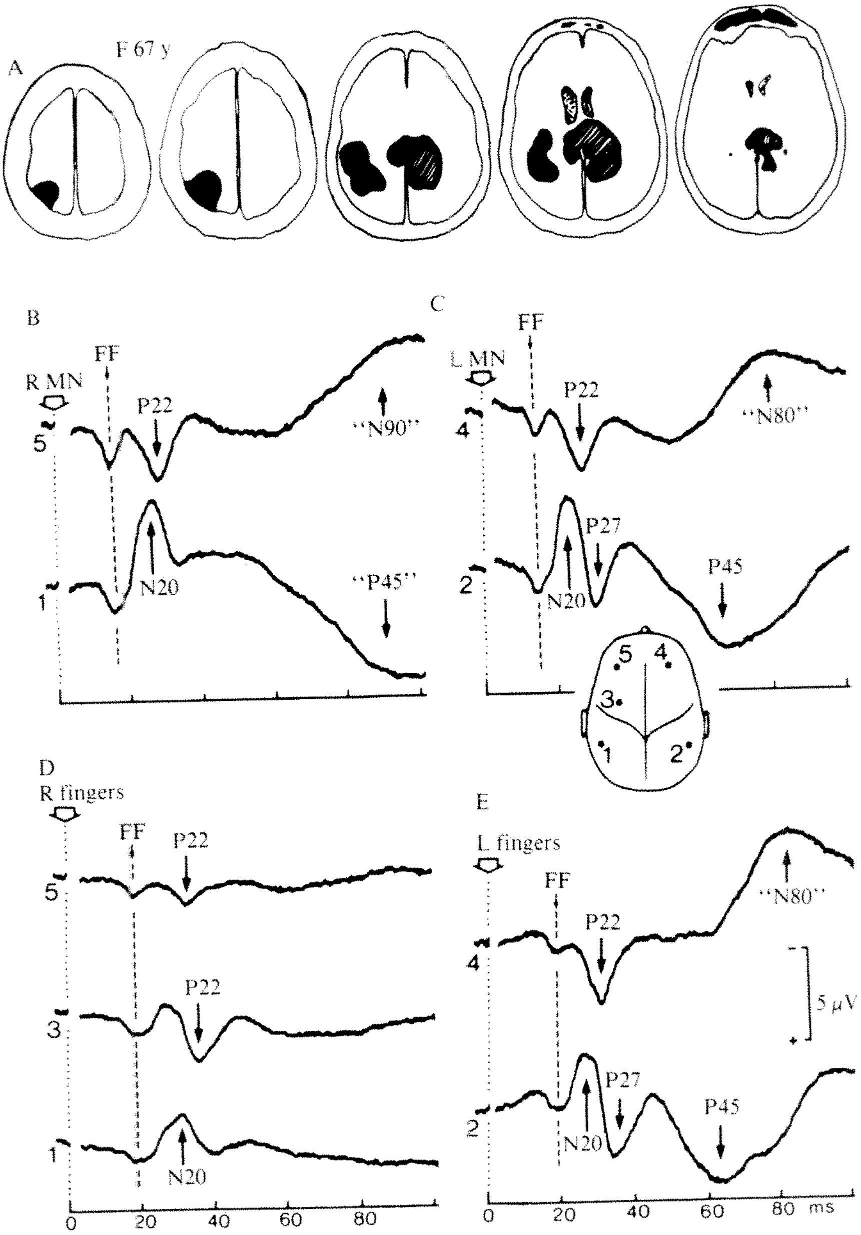

FIG. 10. *Case 13*, female aged 67 years, with a large cerebral tumour (A). Electrical stimulation of the median nerve (B, C) or of fingers II-III (D, E) on the right side (B, D) or on the left (C, E).

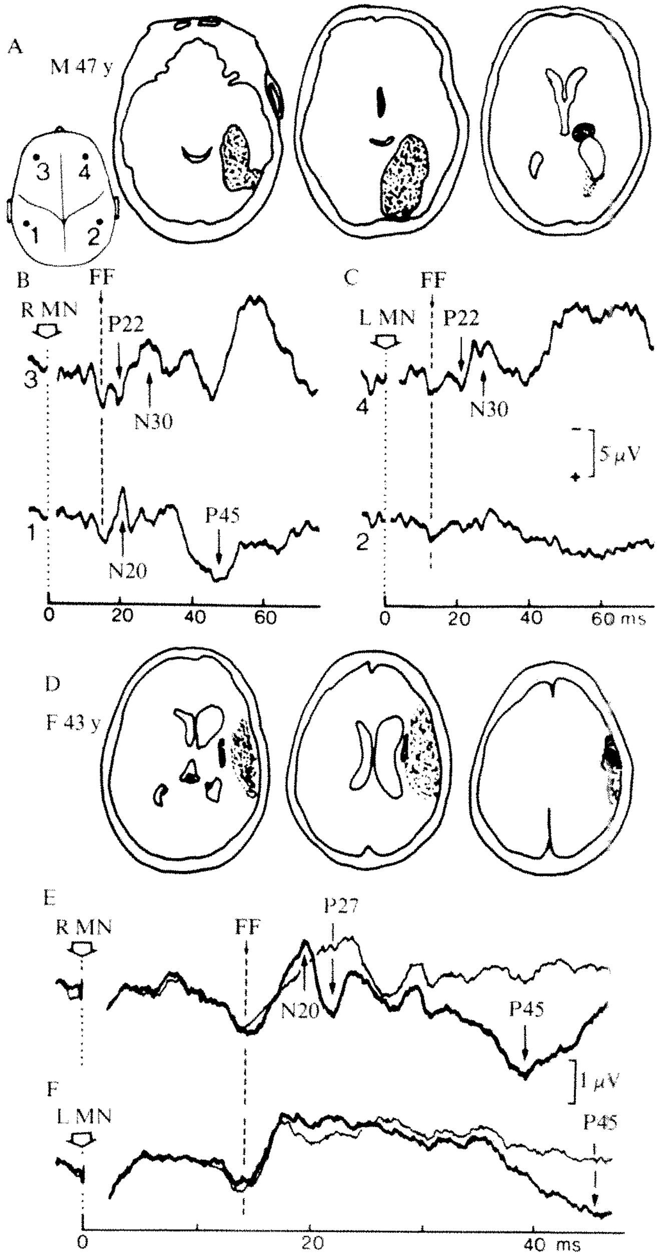

FIG. 11A–C, *Case 14*, male aged 47 years; five years after a right cerebrovascular lesion (A). D–F, *Case 15*, female of 43 years, six years after operation for an intracerebral haematoma. In E and F, the parietal SEP contralateral to the stimulus (thicker trace) is superimposed on the SEP simultaneously recorded ipsilaterally.

Case 15, a female aged 43 years, presented in 1973 with a sudden left hemiplegia with transient anosognosia due to a frontoparietal intracerebral haematoma which was treated surgically. At the time of the SEP study in 1979, a CT scan showed right temporoparietal atrophy with dilatation of the lateral ventricle (fig. 11D). There was complete astereognosis in the left hand and loss of graphaesthesia, but no tactile extinction; tactile, pain, temperature and vibration sense were normal. The tendon reflexes were brisk on the left, but there was no Babinski sign nor any motor deficit. Electrical stimulation of the median nerve on the affected side elicited a normal far field P14, but no early parietal N20-P27 and a reduced and delayed P45 (fig. 11F). Similar stimulation on the normal side evoked normal N20-P27-P45 responses which happened to be rather small in this subject (E). The superimposition of the contralateral and the ipsilateral parietal records was suggested by Desmedt and Cheron (1981*b*) as an efficient means for revealing the true difference between the contralateral N20 cortical response and the underlying (widespread) N18 negativity. In this method the parietal ipsilateral trace is used in fact as a baseline from which the N20 and P27 components diverge and can be more reliably estimated. For stimulation on the affected side, a prolonged N18 extending from about 18 to 38 ms is observed for both parietal sides which is taken to mean that no early parietal cortical response occurs at the affected hemisphere. This rather long duration of the N18 phenomenon has recently been documented in patients with thalamic lesions by Mauguière *et al.* (1983). The somewhat small N20 rising over the N18 'baseline' on the control side (E) is by no means unusual in normal adult subjects and this can be considered within the normal range (*see* Desmedt and Cheron, 1981*b*). Precentral SEPs were not studied in this patient. The EEG was normal.

Case 16, a male aged 58 years, suddenly developed clumsiness and transient tingling paraesthesiae in the right hand. There was defective visual guidance for both hands in the right visual hemifield which suggested a left posterior parietal lesion. Carotid angiography showed a completely occluded left internal carotid artery. At the time of the SEP study, four months later, the CT scan showed an area of reduced density in the left posterior parietal region (fig. 12A). There was clear astereognosis in the right hand and a loss of graphaesthesia, but no tactile extinction, and the primary somatic sensations were all normal. On stimulation of the right median nerve on the affected side, all parietal components were reduced in voltage but none was selectively lost (fig. 12B). The prerolandic responses were normal, as was the EEG.

Astereognosis with Small Parietal Lesions

Two patients served to document unilateral astereognosis and SEP changes in association with minimal cortical lesions. Case 17, a male aged 31 years, sustained a head injury with a left parietal skull fracture in 1978. At the time of the SEP study eighteen months later, the CT scan showed a small area of reduced density in the left parietal region (fig. 12D). There was complete astereognosis and loss of graphaesthesia in the right hand, while touch, pain, temperature, position and

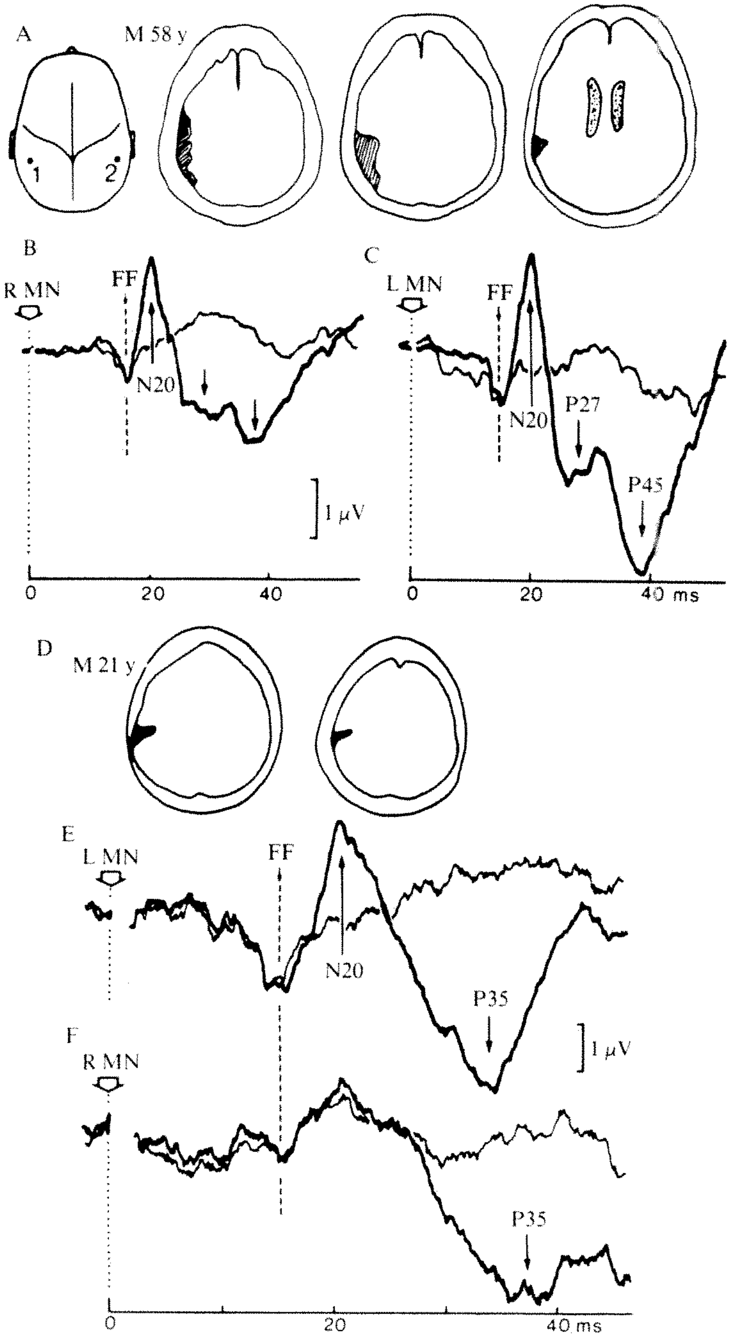

FIG. 12A–C, *Case 16*, male aged 58 years, four months after occlusion of the left internal carotid artery. D–F, *Case 17*, male aged 21 years, eighteen months after head injury with a fracture of the left parietal bone. Stimulation of median nerve. Parietal SEP contralateral to stimulus (thicker trace) superimposed on ipsilateral response.

vibration, sense were normal. There were no abnormal motor signs and no Babinski sign. On stimulation of the median nerve on the affected side, virtually no parietal N20 was detected in comparison with the ipsilateral trace, while the subsequent positivity was delayed and reduced in amplitude (fig. 12F). Stimulation on the normal side elicited a large parietal N20 that was clearly seen on top of the superimposed (ipsilateral) N18 and a P35 (E). The fact that the parietal positivity had a single (P35) peak instead of a 'W' pattern with P27-P45 is not unusual in young adults where it was found to occur in about 50 per cent of normals (Desmedt and Cheron, 1980*b*, p. 418). The EEG was normal.

Case 18, a female aged 36 years, presented in 1979 with a transient right hemiparesis related to an occlusion of the left internal carotid artery (shown by arteriography). At the time of the SEP study, two months later, the CT scan showed a very small left parietal infarct (fig. 13A). There was no Babinski sign and no motor deficit, but brisk tendon reflexes on the right. There was complete astereognosis and a loss of graphaesthesia in the right hand, while tactile two-point discrimination (5 mm) at finger tip and position sense were virtually normal. Vibration, pain and temperature sense were normal. There was no tactile extinction. Stimulation of the second and third fingers on the affected side elicited normal prerolandic P22-N30 responses (fig. 13D3), while the parietal P27 was abolished and the P45 reduced (B). However, the contralateral N20 appeared only slightly reduced with respect to control (C) when closely examined in several trials with the superimposed ipsilateral trace serving as 'baseline'. Here again, the identification of changes in SEP components is obviously assisted by the superimposition of contralateral and ipsilateral traces, and by the consideration of the component's features for stimulation on the control side in the same patient. For example, the parietal P27 can be missing in quite a few normal adult subjects who lack the usual 'W' pattern (Desmedt and Cheron, 1981*b*). Therefore one can only consider that P27 has been lost in conjunction with a parietal lesion (fig. 13B) if it is shown that the patient indeed has a clear P27 on the control side, as in the present case (fig. 13C). The EEG was normal in this patient.

Extensive Unilateral Cortical Lesions

Cases 19 and 20 presented with an acute left hemiplegia with a persistent upper motor neuron deficit, astereognosis, and a complete loss of touch, pain, vibration and position sense. Anosognosia and asomatognosia of the left half of the body occurred transiently in the acute stage. At the time of the SEP study, a CT scan showed an extensive area of reduced density in the territory of the middle cerebral artery related to the ischaemic lesion (fig. 14A, B). On stimulation of the left median nerve, all SEP components were lost after the far field P14 (fig. 13D). Stimulation on the normal side (C) elicited SEPs with a large prerolandic P22 (much larger than the parietal N20 in C1) and a N30 that extended to the ipsilateral front (C6). The cortical auditory potentials studied with the method of Peronnet *et al.* (1974) and Peronnet

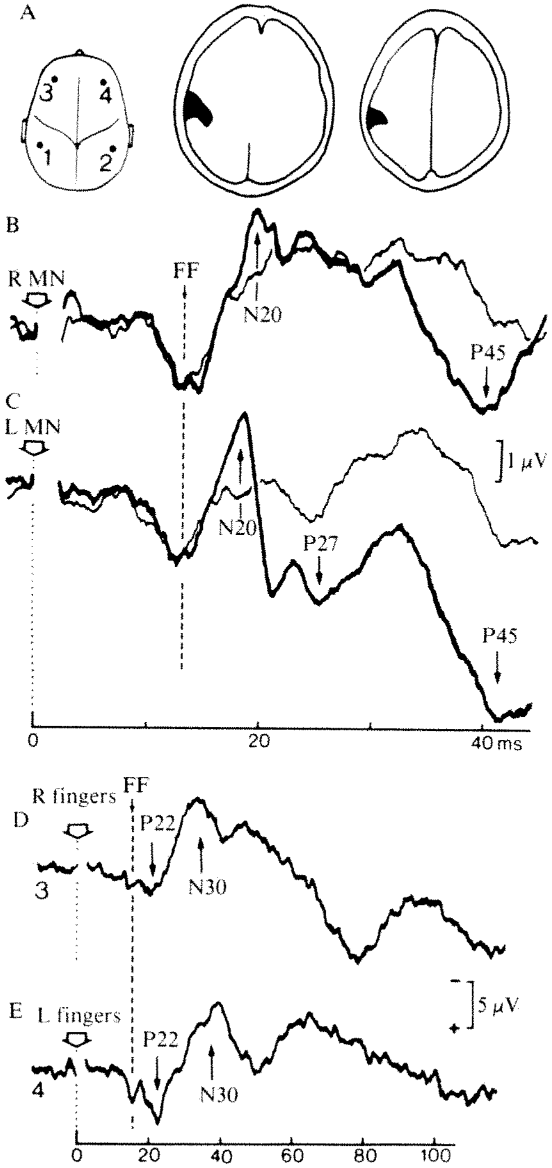

FIG. 13. *Case 18*, female aged 36 years, two months after occlusion of the left internal carotid artery. B–C, electrical stimulation of right (B) or left (C) median nerve. The parietal SEP contralateral to stimulus (thicker trace) is superimposed on the ipsilateral response. D–E, prerolandic responses to stimulation of fingers II-III on right (D) or left (E) side.

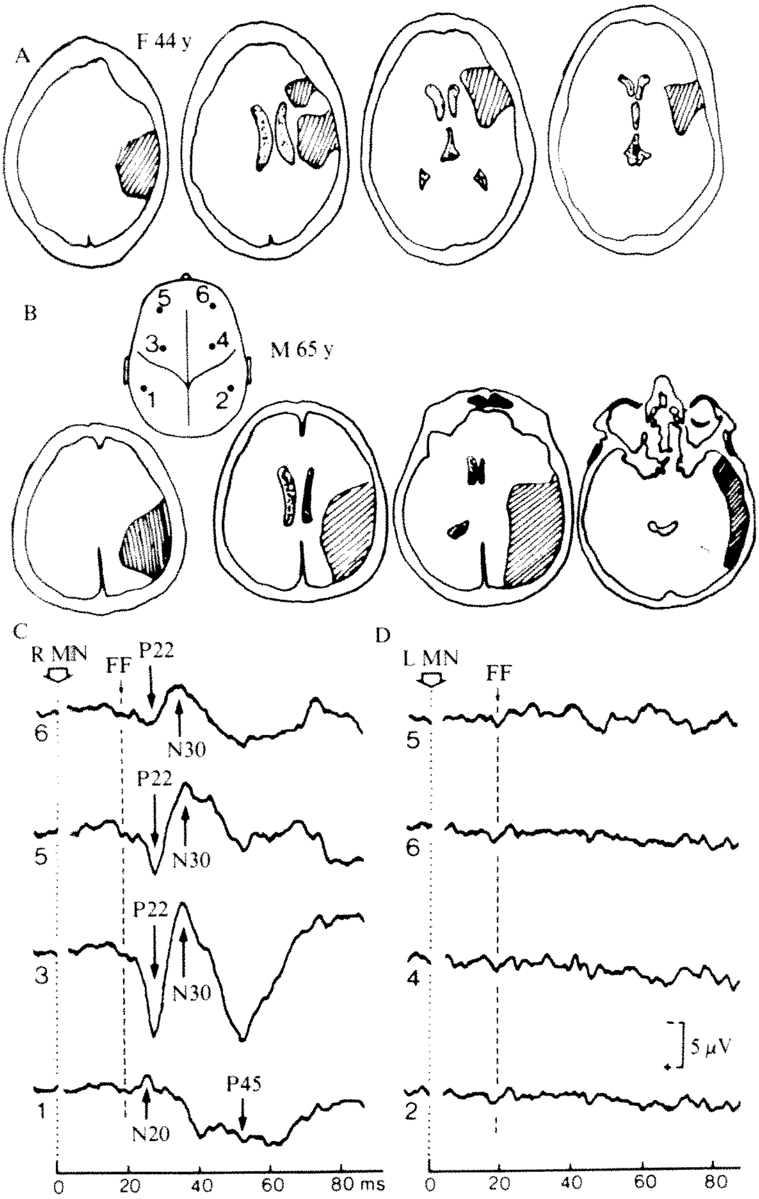

FIG. 14A, CT scan of *Case 19*, female aged 44 years, three years after a right frontoparietal infarct due to occlusion of the middle cerebral artery. B–D, *Case 20*, male aged 65 years, three months after a right parietotemporal vascular lesion. Stimulation of the median nerve on the normal (C) and on the affected (D) side.

and Michel (1977) were absent over the right hemisphere in Case 19, and on both sides in Case 20. The right temporoparietal EEG showed bursts at 3 to 4 Hz in Case 19, and a reduced amplitude without slowing in Case 20.

Unilateral Subcortical Lesions

Case 21, a male aged 60 years, suddenly developed a left hemiplegia with anosognosia and complete sensory loss on the left side. The CT scan showed an extensive subcortical haemorrhage with bleeding into the ventricles (fig. 15A). Two months later, stimulation of the median nerve on the normal side evoked the usual

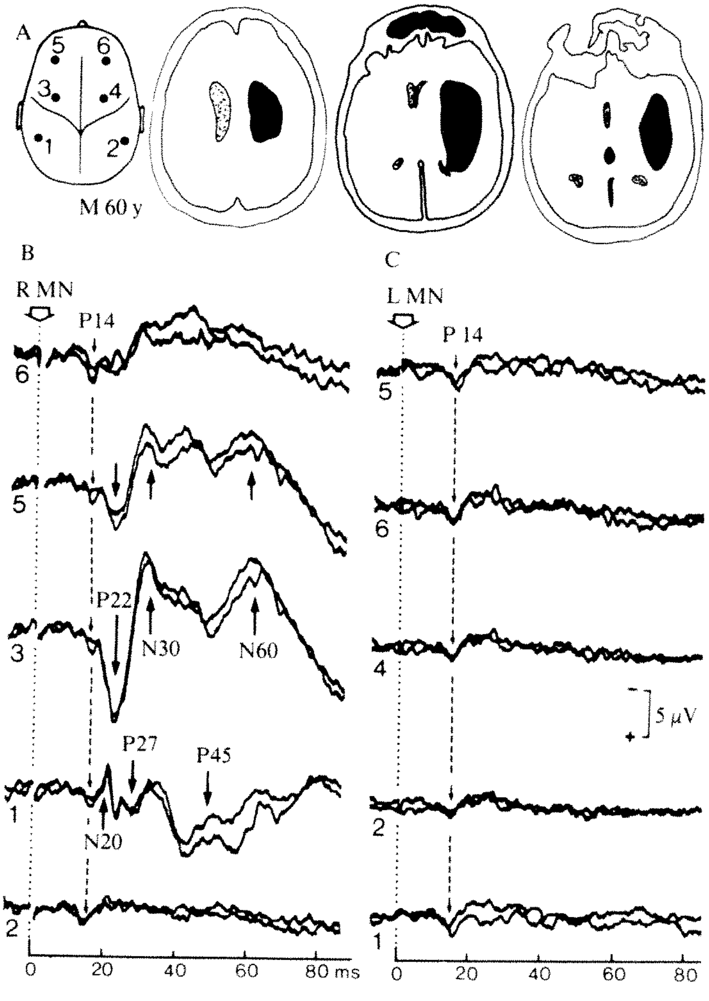

FIG. 15. *Case 21*, male aged 60 years, two months after an extensive right subcortical haemorrhage. Stimulation of the median nerve on the normal (B) and on the affected (C) side. Two independent averages are superimposed for each site in order to show the consistency of waveforms.

SEP components (B1, B3, B5), including an ipsilateral frontal N30 (B6). Similar stimulation on the affected side elicited no response after the far field P14 (fig. 15C). The EEG showed frequent slow bursts at 3 to 4 Hz over the right hemisphere. The statement that *late* ipsilateral SEPs disappear together with contralateral responses after severe unilateral lesions (Liberson, 1966; Williamson *et al.*, 1970; Tsumoto *et al.*, 1973) can thus be applied to the *early frontal* ipsilateral component (*see details* in Desmedt and Cheron, 1981*b*) in our patients (figs 1, C7; 3, C5; 6, C5; 14, D5; 15, C5). This point deserves to be made even though we do not wish to take issue with the problem as to whether the N30 recorded over the front ipsilateral to the side stimulated may be mediated either *via* callosal connections from the contralateral hemisphere, or through volume conduction of the contralateral N30, or both.

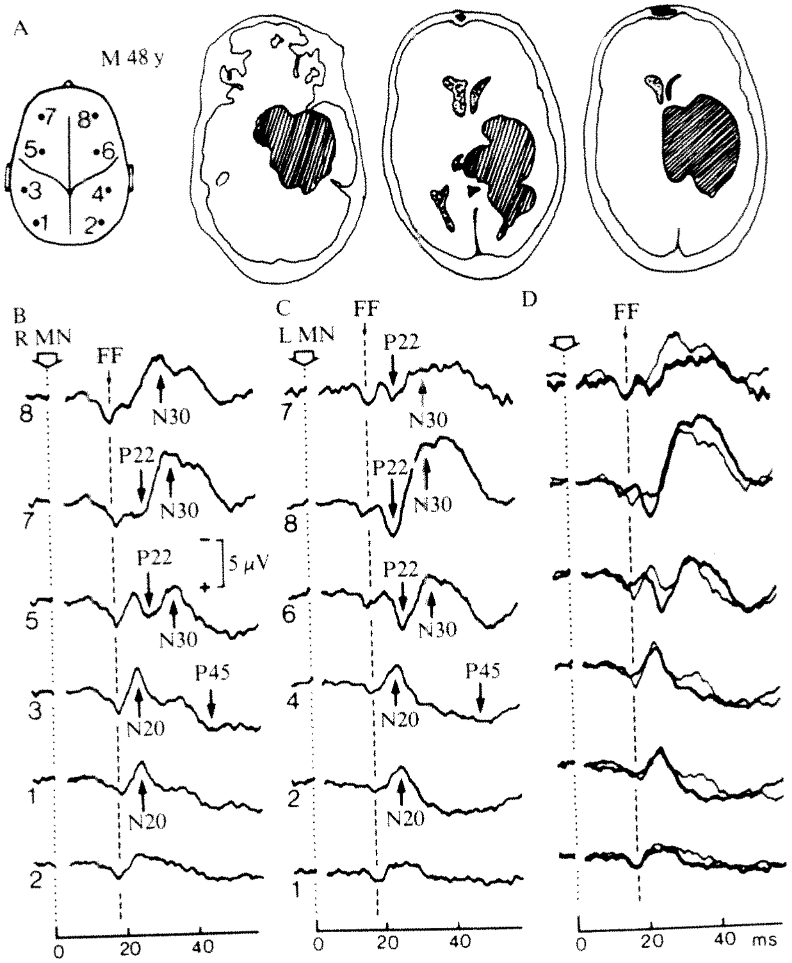

FIG. 16. *Case 22*, male aged 48 years, with a slowly growing epidermoid cyst. Stimulation of the median nerve on the right (B) and on the left (C) side. The traces are superimposed in D, as in fig. 3.

The question as to whether a subcortical lesion might affect the prerolandic or parietal SEP components differentially is important, but it will not be considered in this paper. We have, however, studied patients with subcortical vascular lesions and clinical astereognosis whose SEPs showed loss of the parietal components, but preservation of the prerolandic P22 component. This suggests that the thalamocortical pathways to areas behind or in front of the central sulcus are anatomically distinct and can be differentially affected by a subcortical lesion.

Slowly Progressive Lesions

Case 22, a male aged 48 years, demonstrated that SEP changes correlate better with the clinical signs than with the CT scan in slowly progressive lesions. He had developed over about four years motor clumsiness of the left arm and leg with a mild left hemiparesis. At the time of the SEP study, the CT scan showed an extensive area of reduced density (fig. 16A) that was later identified at operation as an epidermoid cyst communicating with the lateral ventricle. Stereognosis was good and there was no tactile extinction in the left hand. Touch, pain, temperature, vibration and joint position sense were normal. SEP components were similar with stimulation on either side (fig. 16B, C), but the prerolandic P22-N30 were somewhat larger on the affected side (C6, C8). The good SEP responses contrasted with the extensive CT scan abnormalities, but correlated well with the virtually normal sensation found clinically. The EEG showed occasional right temporal slowing at 6 to 7 Hz.

DISCUSSION

Each of the 24 patients selected for this study presented one stable unilateral lesion and, collectively, the lesions mapped out a variety of cerebral sites from the anterior frontal to the posterior parietal regions. The data provide the first detailed case by case analysis of dissociated somatic sensory loss in conjunction with the dissociated enhancement or loss of single SEP components and with evidence as to the anatomical location and extent of a single circumscribed cerebral lesion.

Besides documenting the physiological correlates of astereognosis and other clinical signs, the results substantiate the view that the P22-N30 SEP components recorded from the scalp in front of the rolandic fissure and the N20-P27-P45 components recorded from behind the fissure do indeed involve separate neural generators. These SEP components were analysed in detail with a noncephalic reference electrode (Desmedt and Cheron, 1981*b*), but they can also be studied with an earlobe reference electrode which is more convenient to use in some of the patients in whom recording conditions may be suboptimal. The frontal SEP components could not be dissociated from the parietal SEP components in previous studies using electrode montages with a frontal scalp reference in which case the two sets of SEP components are concurrently injected into grids 1 and 2 of the same amplifiers. A complete loss of either the parietal or the prerolandic early cortical components in focal lesions (as in figs. 3, 7 and 8) would not have been revealed by a frontal reference montage since the SEP components remaining at the unaffected scalp site then appear (with inverted polarity) in the composite trace and the loss of one set of cerebral SEP generators is overlooked. This issue in relation to recording methods has frequently been neglected, yet it is essential for correctly interpreting SEP data in patients with focal cerebral lesions.

Early Cortical SEP Components

In this discussion, the N20 SEP component recorded from the parietal scalp contralateral to the hand stimulated is considered to be the earliest cortical reponse of the somatosensory receiving cortex. The prerolandic P22 is also a rather early cortical response which is considered to be generated in the motor cortex (*see below*). However, the onset latency of P22 significantly exceeds that of N20 by a mean of 0.75 ms (Desmedt and Cheron, 1981*b*, Table 3; this paper, Table 2).

TABLE 2. LATENCIES OF SEP COMPONENTS IN PATIENTS WITH CIRCUMSCRIBED LESIONS

Component of SEP	*Normal side (ms)*	*Difference of lesion side (ms)*	*(Paired t-test)*
Onset of P14	12.13 ± 1.77 (n = 18)	+0.103 ± 1.02 (n = 18)	0.673 (n.s.)
Peak of P14	15.6 ± 1.45 (n = 18)	+0.18 ± 0.6 (n = 18)	0.249 (n.s.)
Onset of N20	17.97 ± 1.56 (n = 18)	+0.11 ± 0.668 (n = 14)	0.564 (n.s.)
Peak of N20	21.3 ± 1.48 (n = 18)	+1.1 ± 1.8 (n = 14)	0.040
Onset of P22	18.73 ± 1.50 (n = 18)	+0.152 ± 0.53 (n = 12)	0.343 (n.s.)
Peak of P22	21.2 ± 1.6 (n = 18)	+1.1 ± 1.8 (n = 12)	0.040
Peak of N30	31.47 ± 3.97 (n = 18)	+1.4 ± 2.28 (n = 11)	0.056

All SEP data for median nerve stimulation at the wrist.

Kritchevsky and Wiederholt (1978), using a noncephalic reference, drew attention to the apparently bilateral distribution of the early SEP negativity, while Chiappa *et al.* (1980, p. 270) found persistence of early negative SEP deflection (with loss of the subsequent P27) in a patient with extensive radiolucent lesions of the centrum semiovale white matter in the CT scan. The latter data suggested that the early SEP negativity was generated in the thalamus or in thalamocortical radiation fibres rather than in the cortex as previously believed (Giblin, 1964; Desmedt and Manil, 1970; Desmedt and Robertson, 1977; Small *et al.*, 1980). A way out of this dilemma was proposed by Desmedt and Cheron (1981*b*) who emphasized the dual nature of the early SEP negativities: they differentiated an N18 component of widespread symmetrical scalp distribution from the classical N20 component which is only recorded over the contralateral postrolandic scalp. Mauguière *et al.* (1983) further showed that the generators of the widespread N18 must be subcortical, since N18 persists in patients with an extensive thalamic or suprathalamic lesion eliminating both the postcentral N20-P27-P45 and the prerolandic P22-N30 SEP components.

Detailed scalp mapping documents the genuine difference of SEP waveforms on either sides of the rolandic sulcus (Desmedt and Cheron, 1980*b*). The restricted distribution of N20 over the contralateral postrolandic scalp and the occurrence of SEP components with different latencies and polarities over the prerolandic scalp support the view that N20 and P22 are generated in the cortex rather than subcortically. All SEP components shown so far to be generated subcortically (P9, P11, P14, N18) present a widespread distribution over the scalp. Furthermore, studies of neuromagnetic fields in adult man suggest that the activity picked up around 20 ms after electrical stimulation of the contralateral median nerve is generated at a depth of about 3 cm from the scalp surface (Kaufman and Williamson, 1982), which implies that the corresponding generators are cortical rather than subcortical. Nevertheless, it must be recognized that such magnetic gradiometer evidence cannot yet answer the question critically as to whether one or more cortical generators may be activated in this time slot. In fact, at the present stage of technical development, such a question can be discussed more critically on the basis of electrical recordings in patients with focal cortical lesions, as reported in the present paper.

Reliability of SEP Features

On electrical stimulation of the median nerve on the *unaffected side* of our patients, the latencies of the SEP components (Table 2) were consistent with another series of normals (Desmedt and Cheron, 1980*b*, 1981*b*). It is well known that the intersubject differences in arm length influence the onset latency of the parietal N20 SEP component (*see* Hume and Cant, 1978; Small *et al.*, 1980). The arm lengths were rather homogeneous in our material and the means showed a reasonably small scatter. We did not include in Table 2 the data for finger stimulation which involve an additional finger-to-wrist conduction time of about 3 ms. The mean interval of 0.76 ms from onset of the parietal N20 to onset of the prerolandic P22 (at frontal recording sites) compares remarkably well with the means of 0.62 ms in young adults and 0.95 ms in healthy octogenarians recorded for the same measure by Desmedt and Cheron (1981*b*, Table 3).

The SEP changes with stimulation on the affected side were unrelated to any peripheral or central conduction disorder up to the thalamus since the far field P14, now considered to be generated in the medial lemniscus (Nakanishi *et al.*, 1978; Arezzo *et al.*, 1979; Desmedt and Cheron, 1980*a*, 1981*a*, 1982; Anziska and Cracco, 1980; Mauguière and Courjon, 1981) presented no significant latency difference with the control side (Table 2). Various lesions involving peripheral nerves or the subcortical pathway are known to increase the SEP onset latencies (Desmedt, 1971; Noel and Desmedt, 1975, 1980; Colon *et al.*, 1977; Mastaglia *et al.*, 1979; El-Negamy and Sedgwick, 1979; Anziska and Cracco, 1980; Eisen and Odusote, 1980; Chiappa *et al.*, 1980; Jones and Halliday, 1982).

The characteristic feature in patients with cortical lesions, however, is that the onset latency is either equal to control or only slightly increased (Table 2), while the changes in amplitude or duration of cortical SEP components may be rather marked (*see* Shibasaki *et al.*, 1978; Halliday and Halliday, 1980; Noel and Desmedt, 1980; Mauguière *et al.*, 1982).

In the present study, the normal side of each patient served as his or her own control so as to detect small abnormalities and to minimize the problems associated with the rather wide intersubject variations in the amplitude of SEP components. Superimposition of the contralateral parietal SEP response on the ipsilateral parietal trace sometimes proved essential for a critical assessment of changes affecting the contralateral N20-P27 (*see* discussion of this method in Desmedt and Cheron, 1981*b*), especially in conjunction with 'pure' astereognosis with small postcentral lesions (figs. 11, 12, 13).

SEP differences on stimulation of either the affected or the normal side, respectively, were genuine and unrelated to experimental conditions. For example, the size of the afferent peripheral volleys were presumably comparable on both sides since the median nerve stimuli were adjusted in relation to thumb twitch threshold, and were thus independent of the sensory changes on the affected side. When using finger stimulation, we compared different intensities in independent runs on either side so as to assess whether the changes in SEP responses occurred consistently, irrespective of the use of any particular intensity (figs. 3, 7).

In patients with vascular lesions, the time interval between the initial lesion and the SEP study (two months to five years) was sufficient to exclude acute local changes and oedema. The SEP and clinical data were always compared after the lesion had stabilized. Distant distortions from a large space occupying lesion may have affected SEPs in Case 13 (fig. 10). On the other hand, a large slowly expanding tumour was found to have little effect on the SEPs in Case 22 (fig. 16).

In Cases 1 and 6, who had had recent craniotomies, the recording electrodes were placed at a distance of over 5 cm from bone flap in order to avoid effects related to the skull defect. The focal EEG slowing recorded in several patients would presumably influence the later components of the averaged responses, but in the present study this did not affect evaluation of changes in the *early* SEP components. These are usually not susceptible to slow EEG waves, especially when a sufficient number of trials (at least 500) are averaged.

Prerolandic and parietal SEP generators. Cerebral lesions destroying the anterior parietal cortex resulted in contralateral hemianaesthesia without hemiplegia and eliminated the N20-P27-P45 SEP components recorded over the parietal scalp; they did not reduce the prerolandic P22-N30 SEP components which unexpectedly tended to increase in voltage with respect to the control responses (figs. 7, 8, 9). On the other hand, the P22-N30 components must be generated in the more posterior part of the frontal cortex (*see* below) since they were not reduced nor eliminated by anterior frontal lesions rostral to the anterior horn of the lateral ventricle (figs. 1, 2). These data raise important issues as to the functional significance of the short latency prerolandic SEP generators for somatic sensation and for motor control.

In awake monkeys performing voluntary movements, the pyramidal tract neurons of motor area 4 are controlled by feedback through sensory inputs from the moving arm (Evarts and Tanji, 1976; Evarts and Fromm, 1978; Conrad, 1978) (*via* the dorsal column pathway (*see* Marsden *et al.*, 1978). These data are in line with the concept of momentary motor control through a transcortical servo loop (*see* Phillips, 1969) involving computation of mismatch between actual and intended movement (Evarts and Fromm, 1978). Besides proprioceptive inputs from active muscles, the inputs from skin and joints are important for finger and hand movements. The finding that electrical stimulation of fingers (thus excluding group I afferents) elicits large prerolandic responses (Desmedt and Cheron, 1980*b*, 1981*b*) (figs. 7D; 8, 9D, 15B) is in line with the presence in the motor area 4 of the monkey of a sizeable population of neurons that respond with very short latency either to skin or joint inputs from the contralateral hand (Rosen and Asanuma, 1972; Lemon and Porter, 1976; Wong *et al.*, 1978; Strick and Preston, 1978; Lemon, 1981; Tanji and Wise, 1981). Activities of the hand-input neurons are modulated during fractionated digit movements rather than during power grip (Lemon, 1981).

Direct anatomical projections reach the motor cortex from thalamic ventroposterolateralis pars oralis (VPLo) neurons which in turn receive short latency inputs from nerves of the arm and thus transmit these signals to the cortical motor area of the arm (Lemon and van der Burg, 1979; Horne and Tracey, 1979; Asanuma *et. al.*, 1980). The response of the motor cortex neurons can be eliminated by section of the dorsal columns (Brinkman *et al.*, 1978). However, tracer studies involving concurrent HRP and tritiated amino acid injections into VPLo showed that the VPLo neurons projecting to the motor cortex fail to receive direct inputs from the dorsal column nuclei (Tracey *et al.*, 1980). It is uncertain whether spinothalamic inputs could arrive in time in VPLo to account for the early VPLo responses; in any case, the experimental transection of the dorsal columns which abolishes these reponses could not interfere with the spinothalamic route (Brinkman *et al.*, 1978). The deep cerebellar nuclei project heavily on to VPLo (Tracey *et al.*, 1980), but the neurons of these nuclei show long latency and uncertain responses to peripheral stimuli (Allen *et al.*, 1977; Harvey *et al.*, 1979). Furthermore, cerebellar ablations do not appear to reduce the area 4 responses (Malis *et al.*, 1953). Further anatomical studies may elucidate how dorsal column inputs reach VPLo neurons to be rapidly projected to motor area 4 (*see* Jones, 1983).

An alternative explanation would be that short latency lemniscal inputs reach the motor cortex, not *via* the motor thalamic relay in VPLo, but indirectly *via* the parietal cortex. The lemniscal somatosensory relay through the pars caudalis of VPL (VPLc) projects to areas 3-1-2 in the postcentral gyrus (Jones and Powell, 1970; Jones *et al.*, 1979). Neurons of areas 3 and 1 project backwards to area 2 which in turn sends direct projections to neurons of motor area 4 (Jones *et al.*, 1978; Strick and Kim, 1978; Jones, 1983). In the monkey, the motor cortex responses to somatic inputs may be supported at least in part through this route.

The SEP data in our patients are pertinent to these current issues. The prerolandic P22 SEP component persisted with its usual short latency (Table 2) in postcentral cortical lesions that eliminated the early parietal responses (Cases 10, 14). Therefore P22 cannot be interpreted as a mirror image (phase reversal) of the parietal N20 (as suggested by Broughton, 1969), and it must involve a separate precentral generator (Papakostopoulos and Crow, 1980; Desmedt and Cheron, 1980*b*, 1981*b*). Moreover, these results appear to establish that the prerolandic P22 generators can be activated in man through a direct thalamocortical pathway, independently of the corticocortical pathways from parietal area 2 (and 5; *see* Jones and Powell, 1970) to area 4. The fact that the latter corticocortical connections are evidenced by robust anatomical data (*see* Jones, 1983) does not imply that a direct thalamocortical route to the motor cortex is not present. Another point is that the interval between onset latencies of N20 and P22 is only 0.6 ms (Desmedt and Cheron, 1981*b*; *see also* Table 2). This significant, but brief, interval barely provides enough time for conduction along the less direct route *via* the parietal cortex (N20 onset latency indicates the arrival time at the parietal receiving areas) (Desmedt and Cheron, 1981*b*). We do not exclude the indirect corticocortical route as contributing to the prerolandic reponse in the intact brain. The relative functional roles of the two pathways to the motor cortex are still uncertain.

In Cases 10 and 14 with a fairly complete longstanding parietal cortical lesion, it is possible that the corresponding thalamic projection nucleus VPLc has undergone alterations such as retrograde degeneration. The recording of large prerolandic SEP components in these patients is therefore all the more significant for suggesting that a separate thalamocortical pathway from VPLo to the motor cortex must be involved to subserve these reponses under such conditions (figs. 7, 11).

In the premotor agranular cortex of area 6 (including the supplementary motor area), few movement-related neurons seem to have clear peripheral receptive fields (Brinkman and Porter, 1979, 1983; Wise and Tanji, 1981; Jones, 1983). Short latency responses to somatosensory inputs would indeed appear as a feature of some of the motor area 4 neurons, but not of the premotor area 6 neurons. It is thus proposed that the prerolandic P22 of the human SEP is generated in area 4, at least for its initial part. This correlates with the fact that the precentral lesions eliminating P22 are usually associated with a severe hemiplegia (figs. 3, 4, 6; Table 2). Moreover P22 reappeared in conjunction with the clinical regression of the motor deficit after surgical excision of the tumour in Case 6. Thus the prerolandic SEP undergoes alterations that seem to parallel impairment of central motor control.

Changes of latency and/or voltage of N30 are sometimes dissociated from those of P22 (fig. 10D). Also N30 is more vulnerable than P22 in the course of ageing (Desmedt and Cheron, 1980*b*, fig. 4; 1981*b*). N30 generators are not clear; they may in part be in premotor areas which receive connections from area 4 and also from parietal areas (Jones and Powell, 1970; Chavis and Pandya, 1976; Jones, 1983). No firm statement should be made at this stage except that N30 generators do not seem to be located in prefrontal cortex (fig. 1). An N30 is usually seen at the ipsilateral scalp (fig. 1, B8) which disappears along with the contralateral N30 in patients with a severe prerolandic lesion (figs. 3, C5; 6, C5; 14, D5; 15, C5). The ipsilateral N30 may thus be elicited through callosal connections from the side opposite to the hand stimulated.

The N20 and P27 generators in the anterior parietal cortex can be eliminated separately or together by very small cortical lesions (figs. 12D; 13).

Enhancement of SEP components. The remarkable increase in voltage of the prerolandic P22-N30 components in patients with chronic (nine months to five years) parietal lesions (figs. 7, 8, 9) may be related to a phenomenon of 'sensitization' by chronic deafferentation of the motor cortex through degeneration of the corticocortical connections from areas 2 and 5. An additional possibility is that the postcentral cortical lesion would result in changes of the functional organization in the VPLo relay neurons projecting to the motor area. The P22-N30 components may also be enhanced after a chronic prefrontal lesion. They were similar to control in Case 1 with a very recent prefrontal lobectomy (fig. 1), but were enhanced in Case 5 who was studied three years after a prefrontal vascular lesion (fig. 2D).

In cats with experimental chronic partial cortical deafferentation, the cortical responses to residual inputs were only enhanced with respect to control after a delay of two to three months (Franken and Desmedt, 1957; Desmedt and Franken, 1963). A possible mechanism is that the synaptic sites vacated by the degeneration of, say, corticocortical connections, are reinnervated collaterally by intact afferent fibres, but other mechanisms may also be involved (Bach-y-Rita, 1972, 1983; Guth, 1974; Cotman and Lynch 1976; Raisman, 1978; Tsukahara, 1981). For example, neurons of motor area 4 deprived of corticocortical connections through a lesion destroying parietal cortex might receive an additional innervation through newly formed collaterals of the thalamocortical VPLo axons. This is one mechanism whereby a reinforcement of the response to somatosensory inputs could be achieved. The enhanced prerolandic responses do not appear to subserve any conscious somatosensory experience in the patients (such as Case 10) with an absent parietal SEP and hemianaesthesia. Their functional significance is still unclear.

Enhanced prerolandic SEPs can sometimes be conducted backwards by volume conduction along the scalp to be picked up at electrodes over the (inactive) parietal cortex (fig. 7, B1). Reciprocally, when the prerolandic responses are removed by a cerebral lesion, the parietal SEP components can be conducted forwards by volume conduction (fig. 6, C4). These effects need to be considered when interpreting average SEPs, and the use of a number of scalp derivations as in the present study is helpful for resolving such issues.

SEP and primary somatic sensation. The present data agree with previous reports (Halliday and Wakefield, 1963; Giblin, 1964; Noel and Desmedt, 1975) that the parietal N20-P27-P45 SEP components are unchanged in patients with loss of pain and temperature sensation. Conversely, these components may be lost in patients with cerebral lesions that do not give rise to any clinically demonstrable loss of pain and temperature sensation (Cases 11 and 14). The sensory input *via* the lemniscal pathway thus appears essential for generating parietal SEPs.

In a study of subcortical lesions, Tsumoto *et al.* (1973) suggested that the N20-P27 parietal components were related to position and vibration sense, but their material did not include patients with isolated loss of position sense or patients with lesions restricted to the cerebral cortex. We must disagree with their conclusion since the parietal N20-P27 responses were absent in Case 11 with loss of position sense but preserved vibration sense. Our data concur with Roland and Nielsen (1980) who noted that lesions of the postcentral gyrus did not alter the vibration sense threshold (Cases 11 to 18). Indeed, a loss of vibration sense was only found in Case 10 with an unusually complete parietal cortical lesion. We thus agree with the general statement of Holmes (1919) that 'tuning fork tests are among the least useful in cases of cortical disease'.

However, we disagree with Roland and Nielsen's suggestion that vibration sense is subserved by frontal cortex since the prerolandic P22-N30 SEP components were not only preserved but even enhanced in our Case 10 with a complete loss of vibration sense. This rare case of a complete parietal cortical lesion (with loss of vibration and the other primary somatic sensations) without any central paresis or motor signs (fig. 7) provides critical evidence that the lemniscal projections to prerolandic cortex do not subserve any of the conscious somatic sensations.

Astereognosis. Whereas the primary somatic sensations imply detection of mere presence of a single submodality input, the tactile recognition of objects or stereognosis involves the processing of spatial somatosensory inputs over time. Astereognosis in the hand has been associated clinically with direct damage or undercutting of the anterior part of the middle third of the contralateral postcentral gyrus (Roland, 1976), or with surgical excision of the postcentral gyrus (Corkin *et al.*, 1970). Stereognosis was of course abolished in patients with reduced or absent tactile sensation due to massive lesions (Cases 10, 21) (*see* Dejerine, 1914; Kennedy, 1924; Lange, 1936; Nielsen, 1962). Genuine astereognosis, however, implies a loss of tactile recognition of objects in spite of preserved tactile and joint position sense. Graphaesthesia also involves pattern recognition but without active touch, and it was lost in all our patients with astereognosis.

Case 15 presented fairly pure astereognosis after an intracerebral haemorrhage. The CT scan provided no indication as to the precise anatomical subregion involved (fig. 11D), but the parietal N20-P27 SEP components were virtually abolished (fig. 11F). In Case 16 with astereognosis and a somewhat extensive lesion, the postcentral SEP components were not abolished and only showed a reduction in voltage (fig. 12B). More critical evidence is provided by Cases 17 and 18 in whom a very small postcentral lesion produced a lasting pure astereognosis and loss of graphaesthesia in conjunction with a clear reduction or abolition of the N20-P27 components (figs. 12F, 13B). The parietal P45 was less critically involved in these cases with astereognosis. It was delayed in the recordings shown in figs. 10, B1-D1, 11F and 12F, but not in figs. 12B and 13B.

Thus genuine astereognosis appears to be associated with characteristic changes of the parietal SEP components. It correlates with a reduction or abolition of the early N20 cortical response and with a reduction or delay of the early parietal positivities. These SEP changes may not permit any precise delimitation of the critical cortical lesion, but at least they suggest a disorder in the cortical transmission of excitation within the primary receiving areas 3-1-2 of Brodmann and/or from there towards higher order parietal areas. The parietal N20 SEP component representing the earliest cortical response to the afferent lemniscal volley (*see* Desmedt and Cheron, 1981*b*) has not been related to any single cytoarchitectonic area of the postcentral gyrus. Furthermore, small inflections of the N20 profile may suggest that more than one postcentral generator is actually involved. If the latter were to be related to different subareas of the postcentral cortex, the alterations of N20 recorded in patients with astereognosis might well reflect disorders of corticocortical conduction between areas 3, 1 and 2. Alterations of SEP component P27 which is also generated in the parietel cortex might also be suggestive of defective transmission between areas. Thus the range of N20-P27 changes recorded in our patients with pure astereognosis may be conceived as electrical evidence that transactions between parietal areas would be impaired in one or several of their critical components. On the other hand, we have not yet seen any evidence that astereognosis is related to selective alterations of the later SEP components in the presence of normal N20-P27 responses. Thus we can suggest that the critical lesion must involve connections within and/or from the receiving areas. It is interesting that astereognosis is produced by such lesions without loss of tactile and deep sensation. The latter appear less critically dependent on the detailed connections between the parietal cortical areas. In fact, a quite extensive parietal lesion (Case 10) is required to eliminate tactile, vibration and other primary sensations. On the other hand, we have not seen any patient with loss of tactile and deep sensation due to a cortical lesion in whom stereognosis was preserved. Finally, the prerolandic SEP components are neither delayed nor reduced in patients with astereognosis.

Clinical diagnostic uses of the SEP evidence. The averaging of SEPs assisted the clinical interpretation of lateralized deficits of object naming through palpation. For example, Case 13 had impaired tactile recognition in both hands. The parietal N20-P27-P45 to right sided stimulation showed abnormalities that were in line with the pattern seen in astereognosis due to a parietal lesion (fig. 10B, D). By contrast, the normal parietal SEP components to left sided stimulation was taken to indicate that the right hemisphere could process somatic sensory inputs in order to acquire stereognostic information and that the clinical deficit for object naming in the left hand was related to a disconnection (Geschwind and Kaplan, 1962; Schott *et al.*, 1969), preventing transfer of stereognostic information to the left (language) hemisphere (fig. 10A). This is one example of diagnostic uses of the observed relations between changes of parietal or prerolandic SEP components to definite clinical signs in patients with focal lesions.

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SELECTIVE DISTURBANCE OF MOVEMENT VISION AFTER BILATERAL BRAIN DAMAGE

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SUMMARY

A patient who suffered bilateral posterior brain damage exhibited disturbance of movement vision in a rather pure form. The patient had no impression of movement in depth, and could only discriminate between a stationary and a moving target in the periphery of her otherwise intact visual fields. She had some movement vision in the central part of her visual fields, provided that target velocity did not exceed 10 deg/s. Neither did she possess visual movement after effects nor apparent (*phi*) visual movement. In addition, visually guided eye and finger movements were impaired. In contrast to the disturbance of movement perception in the visual modality, movement perception elicited by acoustic and tactile stimuli was not impaired.

On the basis of the localization of the cerebral damage (as judged by CT scanning and neuropsychological testing) it is concluded that the observed disorder in movement vision is due to bilateral cerebral lesions affecting the lateral temporo-occipital cortex and the underlying white matter.

The selectivity of the visual disturbance supports the idea that movement vision is a separate visual function depending on neuronal mechanisms beyond the primary visual cortex.

INTRODUCTION

Reports about selective disturbance or even loss of visual functions after cerebral damage in humans are rare and are mainly limited to single case studies. One explanation for this was given by Campbell at the beginning of this century in his *Histological Studies on the Localisation of Cerebral Function*: 'It is almost impossible for nature to restrict a damaging lesion to the cortex, and to the cortex only, in question' (1905). It is not surprising, therefore, that the idea of a functional organization of the human visual cortex, as proposed, for example, by Reinhard (1887), Riddoch (1917) and Best (1919), has been questioned. Patients suffering from occipital lobe damage usually demonstrate more than one visual function disturbed or lost. However, observations on single cases with bilateral circumscribed damage in the posterior part of the brain showed that the perception of colour or movement, for instance, may be selectively disturbed. While the occurrence of central achromatopsia seems rather well established (for review, *see* Meadows, 1974), reports on specific disorders of the perception of movement are scarce (Pötzl and Redlich, 1911; Goldstein and Gelb, 1918) and their occurrence has been questioned (Teuber, 1960).

Pötzl and Redlich (1911) reported a 58-year-old patient who, after bilateral damage of the posterior brain, could no longer perceive the movement of visual objects. She described her perceptual experience of a moving target as if the visual stimulus remained stationary but appeared at different successive positions. This patient showed in addition a severe restriction of her visual field and an anomic aphasia. Form and colour vision were not disturbed. Goldstein and Gelb (1918) tested their patient (a 24-year-old man who suffered a gunshot wound in the posterior brain) more systematically using a variety of experimental techniques. Besides a bilateral concentric loss of visual field beyond 30 deg eccentricity, this patient demonstrated a complete inability to identify visual objects by their proper names. Visual acuity, colour vision and (nonverbal) discrimination of simple forms (circles, triangles) were normal. When confronted with a moving visual stimulus, the patient reported no impression of movement. When an object was moved from left to right, up and down or back and forth in front of him, he stated that the object was either left or right, up or down, or front or back, but 'nothing was in between'. This loss of movement vision did not depend on whether the patient fixated the object or kept his eyes fixed. There was no perception of apparent movement. In contrast to the loss of visual movement perception, the patient reported a normal impression of movement after tactile stimulation. In everyday life, the patient 'determined' the motion of objects by acoustic cues, such as by the noise of a train coming nearer, or by the change of a person's position. The authors assumed that the lateral and medial parts of the left occipital lobe were damaged. The bilateral concentric loss of visual field indicates, however, that both occipital lobes were probably affected.

Here we report a patient who showed a similar disturbance of movement perception but in an even more selective form. The observations on this patient strongly support the suggestion that visual movement perception can be selectively disturbed after cerebral damage.

CASE REPORT

The 43-year-old patient L.M. had been admitted into hospital in stupor in October 1978. For three days she had complained of severe headaches, radiating behind the ears and also into the neck; in addition she had suffered from vertigo, nausea and repeated vomiting. Body temperature had varied between 38° and 39° C. Epileptic seizures had not been reported. On admission, lumbar puncture revealed a xanthochromic CSF. There was a bilateral papilloedema. An EEG showed continuous bilateral theta-delta activity in the posterior quadrant, more prominent and of higher voltage on the right. On panarteriography neither an aneurysm nor an arteriovenous malformation was found. The intracranial arteries were slightly narrowed but completely visualized. However, the cortical veins in the temporoparietal region were not filled. Several tortuous collateral venous channels (corkscrew-like veins) descending to the vein of Labbé were present. The veins of Trolard were visible. The parietal segment of the superior sagittal sinus was occluded. Circulation was generally slowed. The neurological symptoms and angiographic findings indicated a superior sagittal sinus thrombosis.

We examined the patient for the first time in May 1980 (about nineteen months after the onset of her illness). She tended to fatigue easily; after half an hour of examination she felt exhausted. Her complaints about memory and concentration problems may be explained by this increased fatiguability. A general slowing of all mental processes was evident during the entire observation period.

Neurological and formal neuropsychological examination did not reveal any paresis, ataxia or akinesia, or ideomotor, ideational or constructional apraxia; there were no somatosensory deficits, including stereognosis. The patient had no difficulty with calculation. Her performances in verbal and nonverbal memory tasks were in the low normal range; topographical memory was excellent. On formal language testing there was a mild anomic aphasia; naming failure involved all modalities equally; reading and writing were normal.

The visual disorder complained of by the patient was a loss of movement vision in all three dimensions. She had difficulty, for example, in pouring tea or coffee into a cup because the fluid appeared to be frozen, like a glacier. In addition, she could not stop pouring at the right time since she was unable to perceive the movement in the cup (or a pot) when the fluid rose. Furthermore the patient complained of difficulties in following a dialogue because she could not see the movements of the face and, especially, the mouth of the speaker. In a room where more than two other people were walking she felt very insecure and unwell, and usually left the room immediately, because 'people were suddenly here or there but I have not seen them moving'. The patient experienced the same problem but to an even more marked extent in crowded streets or places, which she therefore avoided as much as possible. She could not cross the street because of her inability to judge the speed of a car, but she could identify the car itself without difficulty. 'When I'm looking at the car first, it seems far away. But then, when I want to cross the road, suddenly the car is very near.' She gradually learned to 'estimate' the distance of moving vehicles by means of the sound becoming louder.

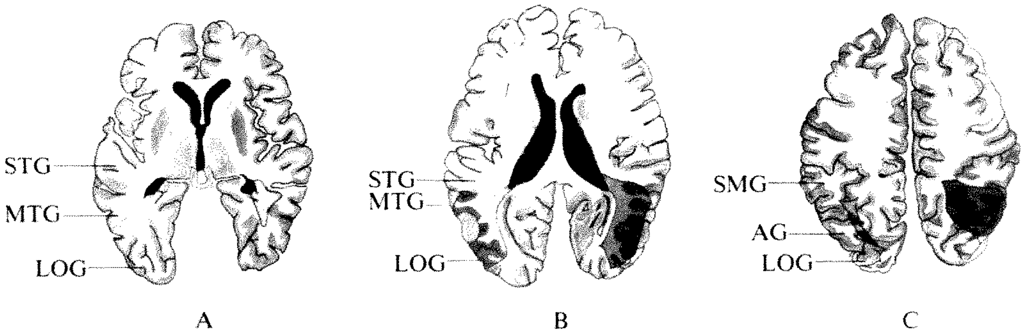

FIG. 1. Diagrams derived from axial CT scans arranged in sequence from A (low ventricular level), through B (high ventricular level) to C (supraventricular level). Hypodense lesions are marked in different shades of grey (slight hypodensities in light dotted grey, marked hypodensities in dark cross-hatched grey. The right-sided lesions are more extensive and more severe than the left-sided lesions. In slice B, a bean-shaped patch is shown on the left side, representing a 'cord sign', which is taken as evidence of venous thrombosis. AG = angular gyrus; LOG = lateral occipital gyri; MTG = medial temporal gyrus; SMG = supramarginal gyrus; STG = superior temporal gyrus.

CT scans had been performed twice, the first in May 1980, the second in December 1981. The findings were identical at both examinations. Those obtained in December 1981 are shown in fig. 1. A slightly hyperdense patch can be observed at the cortical surface of the posterior portion of the middle temporal gyrus. It may be interpreted as a 'cord sign', which is taken as evidence of the thrombosis of cortical veins in cerebral sinovenous occlusion (Buonanno *et al.*, 1978). There were bilateral hypodense lesions in the retrorolandic area, which were more obvious and more extensive in the right hemisphere. Bilaterally symmetrical lesions affected the periventricular segment of the temporoparietal and occipital white matter. They extended into the subcortical white matter and partially into the posterior segment of the middle (and possibly the superior) temporal gyrus, and also into the lateral occipital gyri. On the right the angular gyrus was also involved, whereas on the left a streaky lesion affected the subangular white matter only.

It should be noted that there was a widening of several sulci on the left, especially the postcentral and intraparietal sulci. The lateral ventricles were within the normal size range.

METHODS AND RESULTS

The experimental procedures were performed over a period of three months, nineteen months after the occurrence of the cerebral damage, when neurological and neuropsychological examination was also conducted. About 40 sessions were undertaken during this time. The patient was never informed of the results during or after single experiments. All experiments and tests were carried out at least twice during the examination period. A normal subject (a 24-year-old female) served as a control in most of the experiments. Since the patient tired easily, short breaks (1 to 2 min) were introduced after about 5 min of testing. Instruction was always repeated before restarting the examination.

For greater clarity the observations and experimental results will be presented in four sections: (1) visual functions other than movement vision; (2) disturbance of movement vision; (3) perception of tactile and acoustic motion; (4) the effect of the disturbance and the perception of visual motion on visually guided pursuit eye and finger movements.

Visual Functions other than Movement Vision

Foveal vision. Visual acuity. Distance acuity (Snellen) was 0.8 in each eye; near form acuity was 100 per cent (corresponding to 7 min of arc resolution), and near reading acuity was Nieden 2 (equivalent to 0.3/0.5).

Binocular vision and stereopsis. Binocular vision and simultaneous foveal perception were normal, as were fusion, vergence and accommodation. Stereopsis (as tested with the Titmus and the TNO tests) was normal; stereoacuity was 120 s of arc.

Foveal colour discrimination. For testing foveal colour discrimination the Farnsworth-Munsell 100-hue test was used (Farnsworth, 1943) under binocular viewing conditions. Fig. 2 shows the hue discrimination performance of the patient. Colour discrimination performance was in the lower range according to Farnsworth's classification (mean error rate 1 to 2 errors), but there was no evidence of a colour discrimination deficit (*see* Zihl and Mayer, 1981).

Discrimination of visual stimuli (objects, words). Visual objects or words were presented tachistoscopically and recognition time (for errorless performance) was measured for both subjects. The following stimuli were used: circle, triangle, star, cross, cube; house, apple, horse, tree and face; and 10 words consisting of 4 letters each. Stimulus size was 7.6 deg and letter height 5.7 deg at a viewing distance of 120 cm. The subjects were asked to report what they recognized. Mean recognition time for the patient was 16.0 ms for visual objects (SD 4.7) and 31.2 ms for words (SD 7.5). The normal subject needed 15.4 ms for errorless recognition of visual objects (SD 2.3) and 30.1 ms for words (SD 6.9), respectively. Even though the patient's recognition time was slightly higher for both classes of stimuli, this difference is not statistically significant (t-test; $P > 0.20$).

Visual evoked potentials. Pattern evoked potentials were recorded from a midline occipital scalp electrode placed 1 cm above the inion. A checkerboard stimulus (10 min of arc visual angle; 80 per cent contrast; reversal rate, 2 s, adjusted by a Medelec visual stimulator) was used to evoke the potential under monocular viewing conditions. The signals were amplified, filtered (LF 0.16 Hz; HF 32 Hz) and averaged (64 sweeps) by means of a Medelec system. The patient was asked to look at the centre of the pattern. Monocular pattern evoked potentials were normal with regard to the first prominent positive potential. Latency to peak of this wave was 116 and 117 ms on repetition, after stimulation of the right eye only, and 116 and 118 ms of the left eye, respectively. Peak amplitude was 8.6 and 11.0 μV for the right eye, and 9.0 μV and 10.5 μV for the left eye. These VEP values were in the range for normal subjects tested under similar conditions (*see* Hennerici *et al.*, 1977).

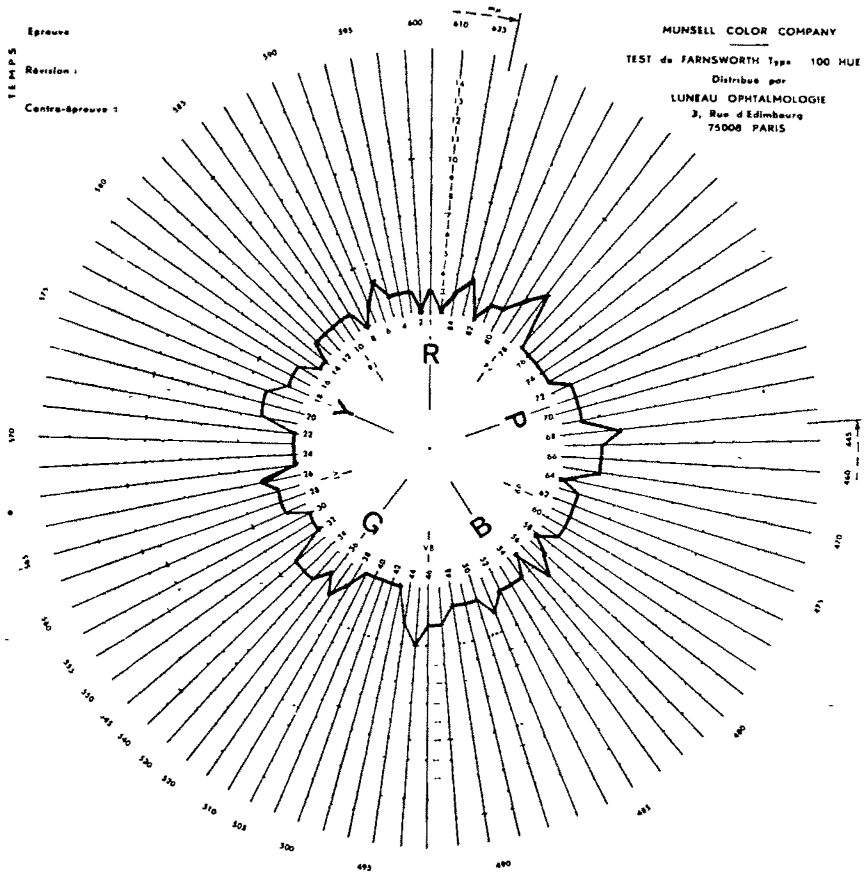

FIG 2. Farnsworth-Munsell 100-hue test (binocular condition) The extent of radial displacement indicates the degree of disturbed hue discrimination in that part of the spectrum R = red, Y = yellow, G = green, B = blue, and P = purple regions of the spectrum.

Visual field testing. The visual fields were mapped for different stimulus dimensions using a Tübinger perimeter (Sloan, 1971). Eye position was monitored by using an infrared camera and a monitor. During perimetric testing, the patient fixated a red spot of light (30 min of visual angle in diameter) in the centre of the perimeter at a distance of 33 cm. Head position was held stable by a chin rest. Background luminance was always 3.2 cd/m^2.

For *dynamic perimetry*, the target (116 min visual angle in diameter) was moved with a constant velocity of about 2 deg/s from the periphery towards the centre of the sphere. The luminance of the target was 320, 3.2 and 0.3 cd/m^2, respectively. The patient was instructed to fixate the red spot in the centre and to press a buzzer-key whenever she detected the light spot. The extent of the visual field was determined for 16 meridians under monocular and binocular viewing conditions.

Fig. 3A shows the binocular visual field and the isopters for target luminance of 320, 3.2 and 0.3 cd/m^2. There was no restriction of the visual field, nor was a scotoma found. The isopters for the dimmer targets showed normal extension in both hemifields.

The profile of the gradient of light sensitivity was measured by means of *static perimetry* under binocular viewing conditions. Light difference thresholds were determined using the method of limits. Target diameter was 69 min of visual angle; presentation time was 500 ms. Target luminance was initially well below threshold and was then increased in steps of 0.05 log units. When the patient detected three targets consecutively, the luminance of the first of these was defined as increment threshold. The profile of the gradient of light sensitivity was determined along the horizontal axis, and is shown in fig. 3B. There was no depression of light sensitivity in either half-field.

In order to test colour identification in the periphery of the visual fields, *colour perimetry* was performed binocularly (Zihl and Mayer, 1981). The coloured targets (blue 480 nm; green 525 nm; red 656 nm) had a diameter of 116 min of arc and were presented with maximum intensity (320 cd/m^2). Each target was shown to the patient before plotting the visual field for that colour by dynamic perimetry (*see above*). The patient's task was to press the buzzer-key whenever she could identify the hue of the target. Fig. 3C shows the fields for the three colours used. When compared with data from normal subjects, there was no noteworthy difference as to the extent of the three colour fields (*see* Zihl and Mayer, 1981).

In addition binocular *form fields* were measured. Circle or diamond targets of different size (luminance 320 cd/m^2) were moved with a low velocity (about 1 deg/s), from the periphery to the centre of the perimeter. The patient was asked to fixate and to press the buzzer-key when she could identify the form of the target by naming. Additionally, binocular visual acuity was measured along the horizontal axis by acuity profile perimetry (Johnson *et al.*, 1979). The test stimuli included seven different sizes of circle and diamond pairs, ranging from 7 min of arc (equivalent to 20/20 Snellen acuity, or 100 per cent relative acuity) to 116 min of arc (20/333 Snellen acuity, or 6 per cent relative acuity). The sequence of the circle and diamond targets

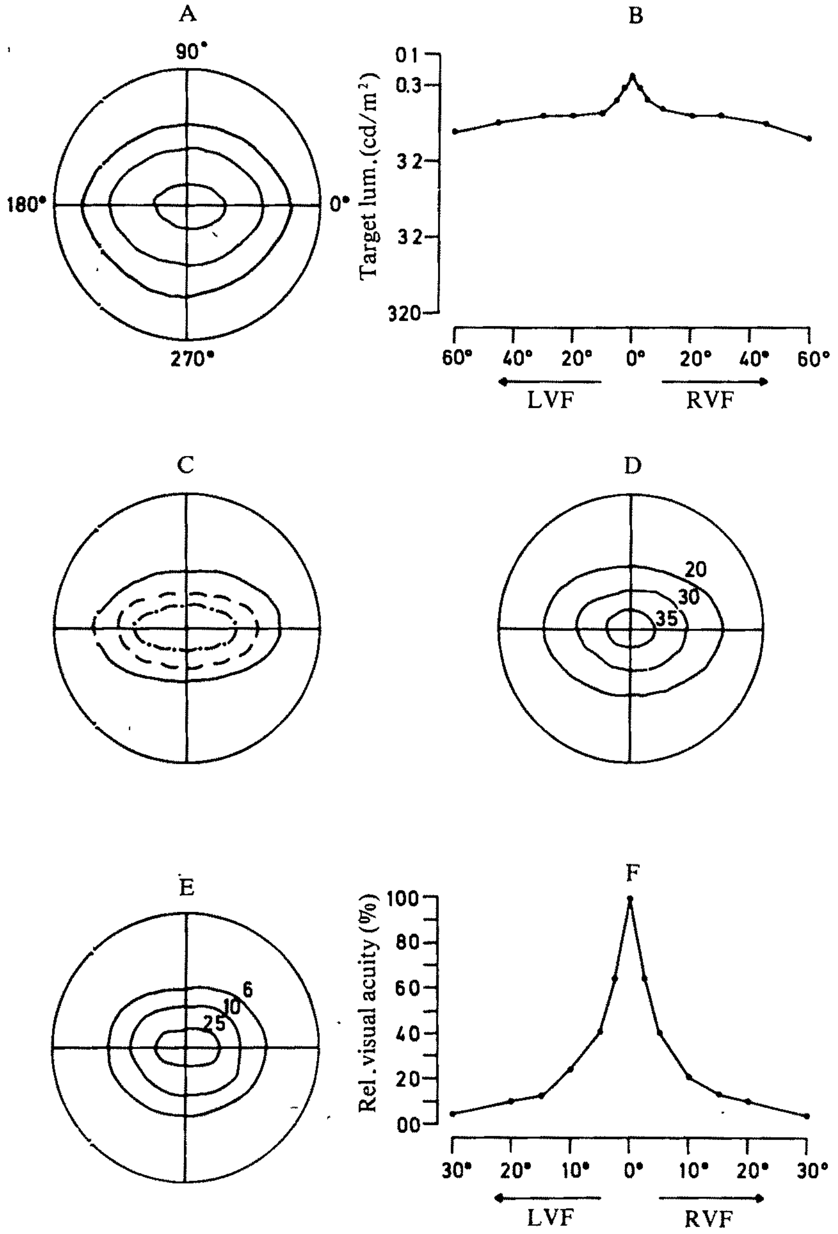

FIG 3 A, Binocular visual fields for white light, C for coloured targets, D flickering targets, and E for forms of different size. Luminance of the target in A was (from outside) 320, 3.2 and 0 3 cd/m². The colour visual fields in C are shown for blue (——), green (- - - -) and red (- · -). CFF-fields in D are shown for targets flickering with 20, 30 and 35 Hz, and form fields in E were measured with targets corresponding to 6, 10 and 25 per cent relative form acuity. In B, the profile of binocular light sensitivity is shown along the horizontal axis. The binocular acuity profile along the same axis is shown in F LVF, RVF = left and right visual fields. For further details, *see text*.

was at random. Target luminance was 320 cd/m^2; presentation time was 1 s. The patient was instructed to keep her eyes on the fixation point (in the centre of the perimeter) and to report which target was presented. Errorless performance (in three trials) was chosen as a criterion for accurate discrimination. Fig. 3E shows the binocular form fields for the identification of three different sizes of the diamond-shaped target (equivalent to 6, 10 and 25 per cent relative acuity isopters). In fig. 3F the acuity profile is shown along the horizontal axis. Both methods revealed normal performance (*see* Johnson *et al.*, 1979).

Critical flicker fusion (CFF) was measured foveally by using a descending method of limits. The patient was asked to press the buzzer-key when she detected the target flickering. In addition, binocular CFF fields were determined by moving the flickering target (flickering rates 20, 30 and 35 Hz) with a velocity of about 1 deg/s from the periphery towards the centre of the perimeter. The patient was instructed to fixate and to press the buzzer-key whenever she detected the target flickering. The boundaries of the CFF fields were determined for 16 meridians. The diameter of the flickering target was 116 min of arc and its luminance 320 cd/m^2.

In fig. 3D the visual field boundaries for targets with different flickering rates are shown. The foveal CFF (mean of 5 values) was 37 Hz (range 36 to 38 Hz). Neither foveal nor peripheral CFF values were significantly depressed when compared with the normal subject (t-test; $P > 0.20$; *see* Table 1).

Double simultaneous stimulation. Detection performance was tested by means of a double simultaneous stimulation technique (*see* Zihl and von Cramon, 1979). Light targets were presented simultaneously either in one binocular hemifield (at 5 and 30 deg eccentricity along the horizontal meridian) or in both half-fields, one in the left and the other in the right field at corresponding positions along the horizontal axis (at 20 and 45 deg eccentricity). Target diameter was 0.5 deg, luminance 1.3 cd/m^2 (contrast ratio to background 13:1) and presentation time 5 ms. Twenty trials were carried out for each condition; intertrial interval was 8 s. The patient sat in a chair at a viewing distance of 120 cm. The targets were presented at

TABLE 1 CRITICAL FLICKER FUSION (TWO MEASUREMENTS) IN HZ AS A FUNCTION OF ECCENTRICITY ALONG THE HORIZONTAL AXIS IN THE LEFT (LVF) AND RIGHT HEMIFIELD (RVF)

	Eccentricity				
	5°	*15°*	*30°*	*45°*	*60°*
LVF					
P	35/34	32/32	30/31	29/29	26/25
N	35/35	32/33	31/30	30/30	26/26
RVF					
P	35/35	33/32	30/30	29/30	25/25
N	35/34	33/33	31/30	30/29	26/25

P = patient; N = normal subject.

eye level. The patient was asked to fixate a red spot of light and to indicate by finger pointing whether she saw one or two stimuli. She was not allowed to make head movements. The patient had no difficulty in detecting both targets in the conditions tested. In at least 18 out of 20 trials she performed correctly. This detection performance does not differ from that of normal subjects under similar conditions (*see* Zihl and von Cramon, 1979). Furthermore, no extinction was observed after prolonged testing in either hemifield.

Saccadic localization. Localization performance by means of sacadic eye movements was tested binocularly for positions along the left and right horizontal meridian. The patient was instructed to look at the fixation point in the perimeter, and to shift her gaze with one sweep towards the left or right side to where she saw a light stimulus. Target diameter was 116 min of arc, luminance 32 cd/m^2; targets were presented for 100 ms.

The amplitude of the saccadic response was judged on the basis of electro-oculographic recording. Electrodes were placed on the lateral canthi, and eye movement responses were recorded by a chart strip recorder (*see* Zihl, 1980, for details). The localization response was defined as the amplitude of the eye movement from the fixation point to the first position of fixation. The correspondence between target and mean eye position (10 trials per position) for 10, 20, 30 and 40 deg eccentricity was fitted by a power curve $y = ax^b$, where b indicates the slope exponent (b = 1 means perfect correspondence). The 'goodness of fit' was determined by the coefficient of determination r^2.

Fig. 4 shows the localization performance by saccadic responses. The correspondence between target and mean eye position was very accurate for both hemifields.

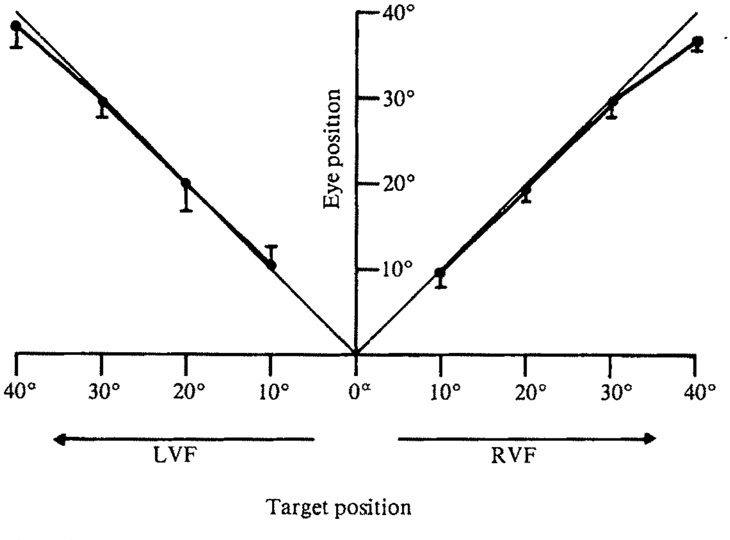

FIG 4. Correspondence between mean eye position (n = 10) and target position along the horizontal axis in the left (LVF) and right hemifield (LVF) Vertical bars indicate half standard errors.

Visual reaction time. Reaction time to light spots was measured along the horizontal axis (binocular viewing condition) by means of an electronic counter (Tectronix DC 503). The onset of the counter was triggered by the onset of the light stimulus. The patient fixated in the centre of the perimeter and was asked to press a button immediately after she detected the light spot. Target diameter was 116 min of arc, luminance 320 cd/m^2 and presentation time 500 ms. The normal subject was tested under the same conditions for comparison.

Table 2 contains the reaction time (mean of 10 measurements; right hand responses) for both subjects. There is no significant difference between the two hemifields of either subject (t-test; $P > 0.20$; all tests two-tailed, if not indicated otherwise), but the values for the patient are significantly higher (t-test; $P < 0.05$). In addition, there is a slight increase of the reaction time with increasing eccentricity for both the patient and the subject. Because of the small number of field positions, the correlation coefficients cannot be interpreted as significant even though the values are relatively high (patient: LVF $r = +0.98$; RVF $r = +0.91$; normal subject: LVF $r = +0.73$; RVF $r = +0.92$).

TABLE 2 MEAN REACTION TIME (IN MS, N = 10) AS A FUNCTION OF ECCENTRICITY ALONG THE HORIZONTAL AXIS IN THE LEFT (LVF) AND RIGHT HEMIFIELD (RVF) FOR PATIENT AND NORMAL SUBJECT

Condition		*Patient*		*Normal subject*	
		Mean	*SD*	*Mean*	*SD*
(A) Fovea		279.8	39.1	227.8	20.7
(B) Periphery					
LVF	5°	266.5	31.5	233.3	18.6
	15°	292.4	40.8	245.0	21.3
	30°	304.3	31.1	252.2	14.2
	45°	333.9	35.8	253.0	15.2
RVF	5°	258.4	28.8	232.8	21.6
	15°	296.8	34.3	241.6	17.6
	30°	308.3	32.9	257.3	14.5
	45°	328.9	37.2	255.3	16.4

Movement Vision

We examined the patient's movement vision using mainly circular light targets. In addition movement after effects and apparent (*phi*) movement were tested. Furthermore, the patient's smooth ocular pursuit and finger pursuit movements were also investigated in order to find out whether motor performance that depended on the perception of visual movement was affected. These tests were performed binocularly. The visual stimuli were always presented approximately on a level with the eyes. Finally, tactile and acoustic movement perception were also tested.

Horizontal and vertical motion. The patient observed a circular spot of light being moved either in the horizontal or vertical direction in front of her. The spot was produced by overhead projection from an optical bench; movement of the spot was achieved by electromagnetic rotation of a prism mounted on the bench. The spot had a diameter of 2.4 deg at a viewing distance of 67 cm. Luminance of the target was 5.2 cd/m^2, background luminance was 0.6 cd/m^2. The path travelled by the light target had a length of 20 deg. The patient either fixated a cross at the midpoint of this path or was allowed to fixate the travelling spot (afferent and efferent motion perception, respectively; *see* Dichgans *et al.*, 1969; Brandt *et al.*, 1973). Velocity of the moving target was adjusted by means of a sine generator in steps of 0.1 Hz (corresponding to 2 deg/s). For any given setting the velocity of the spot was the same at all points on the path, except at the turning points. The patient was asked to report whether (a) she could see clear motion, (b) movement vision was unclear, or (c) no motion could be seen at all.

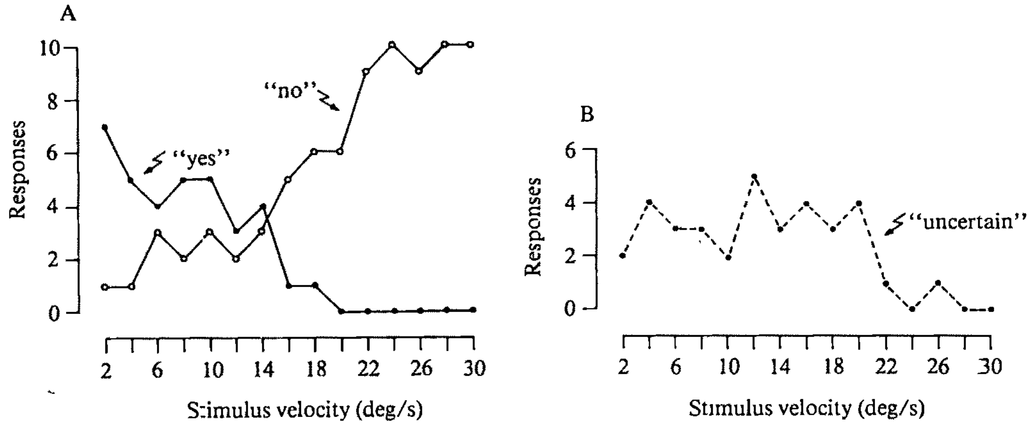

FIG. 5. A, number of 'movement' responses for a target moving in the horizontal direction 'Yes' = clear movement vision, 'No' = no movement vision B, 'uncertain' responses (i e. no clear movement vision)

Fig. 5 shows the number of the three different kinds of responses (10 trials per velocity step) for stimulus velocities between 2 and 30 deg/s in the 'afferent' condition. The patient reported some impression of stimulus movement in the horizontal direction up to a velocity of 14 deg/s. She also had difficulty, however, in seeing movement below this velocity, and up to about 20 deg/s was uncertain whether or not the target moved or was stationary (fig. 5B). When she was allowed to fixate and track the moving spot, she had some movement vision up to about 18 deg/s. The number and distribution of 'uncertain' responses, however, remained quite the same.

For vertical movement direction, the patient could only see the target in motion when stimulus velocity was below 10 deg/s (fig. 6A). 'Uncertain' responses were recorded up to about 16 deg/s; according to the patient's comment, movement vision was also rather unclear for the low velocities (fig. 6B). Again, movement of the target was reported for higher velocity values when the patient could fixate and track the light spot (13 deg/s).

The patient described her perceptual experience for stimulus velocities higher than 18 and 13 deg/s, respectively, as 'one light spot left or right, or up or down, and sometimes at successive positions in between'. When asked to give the order in which the light appeared at successive positions she never confused the positions where she perceived the target as stationary.

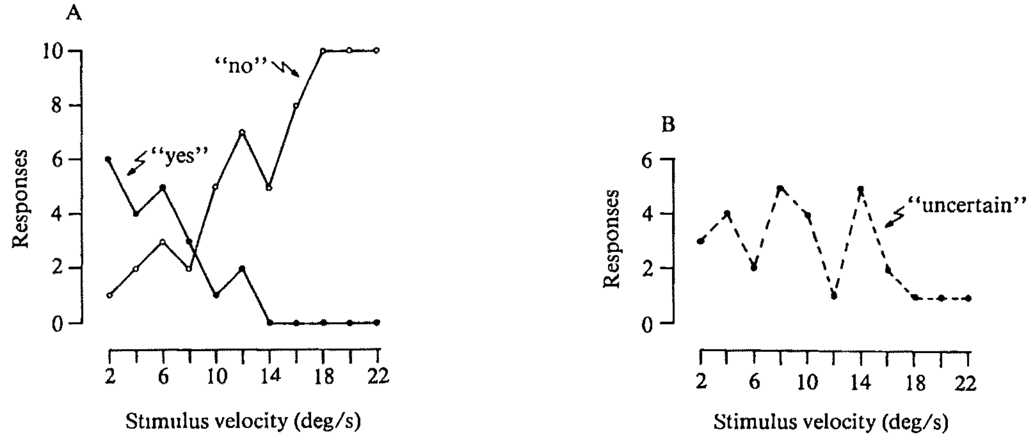

FIG. 6. Number of 'movement' responses for a target moving in the vertical direction Further description as in fig. 5.

Motion in depth. Movement vision in depth was tested monocularly and binocularly by moving a black painted wooden cube on a tabletop. The patient was seated in front of the table. The cube was moved by hand either towards the patient or from the patient in line of sight. Distance of movement was 100 cm (that is, viewing distance varied between 30 and 130 cm); velocity was approximately 3 or 6 deg/s. Even after prolonged testing (after more than 20 trials in each direction) the patient never reported any clear impression of movement. She had, however, a clear impression of change in position and size of the cube, and was able to judge correctly the distance of the cube in relation to other nearby objects.

Detection of movement in the inner and outer visual fields. Perception of movement was tested binocularly for the inner visual field (i.e. up to 15 deg eccentricity) using the Tübinger perimeter. Target size was 116 min of arc and luminance was 32 cd/m^2 (background luminance 3.2 cd/m^2). The target was either presented stationary at 15 deg eccentricity along the left or right horizontal or upper or lower vertical meridians, or was moved with a constant velocity of about 2 deg/s from 15 deg along the above mentioned meridians towards the centre of the visual field. Presentation time was not limited, so that the target was presented until the patient responded. Three different conditions were tested: (a) detection of the stationary target, (b) detection of the movement of the light spot, and (c) detection of the direction of the moving target. All stimulus conditions were shown to the patient and, in addition, 4 to 5 trials were performed before testing. The different test conditions were carried out in different sessions. The patient was asked to fixate the red spot of light in the centre of the perimeter and to press the buzzer-key whenever she could detect the target in the particular stimulation condition. Detection time was defined as time lapse between the onset of presentation and the response of the patient. Twenty trials were carried out in condition (a), while the patient performed 40 trials in the other two conditions, since in about one-third of the trials the patient was not able to decide whether the target was actually in motion or not. Mean detection time in this condition was also calculated on the basis of 20 measurements. Table 3(A) shows mean detection time for the stationary target (presented at 15 deg eccentricity), and fig. 7B for the moving target. Mean detection time for detecting movement of the target was clearly increased in both the patient and the subject, as compared to the mean time needed to detect the stationary target (t-test; $P < 0.01$). In addition, detection time differed for both the horizontal and the vertical axis in both subjects (t-test; $P < 0.01$). The difference in both types of detection (that is, of the stationary and moving targets) between the patient and the normal subject was, however, statistically highly significant (t-test; $P < 0.01$) for targets presented on either the horizontal or vertical axis.

Results regarding detection of direction of movement are shown in fig. 7C. In no condition did the patient perform entirely correctly. Her best performance was 85 per cent correct; performance was significantly better, however, for targets moving along the horizontal meridian than along the vertical axis (t-test, $P < 0.02$). Again, the patient clearly needed more time to detect the direction of movement than the normal subject; the difference is highly significant for both visual axes (t-test; $P < 0.001$). Both the patient and the normal subject, however, needed more time to detect the direction of movement along the vertical axis (t-test; $P < 0.01$).

Detection of the movement in the outer hemifields was tested with the target moving between 40 and 20 deg eccentricity along the horizontal axis, and between 30 and 10 deg eccentricity along the vertical axis. In addition, a stationary target was presented at 40 deg eccentricity (horizontal meridian) and at 30 deg eccentricity (vertical meridian), respectively.

Table 3(B), 3(C) and Table 4 show the mean time for detection of the stationary and moving target in the periphery of the visual field. For both conditions, the difference in detection time differed significantly between the patient and the normal

TABLE 3. MEAN DETECTION TIME (IN MS) FOR A STATIONARY TARGET AS A FUNCTION OF VISUAL FIELD POSITION THE STATIONARY TARGET WAS PRESENTED AT 15 AND 40 DEG ECCENTRICITY ALONG THE HORIZONTAL AXIS, AND AT 30 DEG ECCENTRICITY ALONG THE VERTICAL AXIS

Condition	*Patient*		*Normal subject*	
	Mean	*SD*	*Mean*	*SD*
(A) 15° eccentricity				
Left VF	315.5	32.9	253.9	22.5
Right VF	316.7	38.7	265.6	32.0
Upper VF	400.7	33.9	287.5	35.9
Lower VF	406.3	40.7	282.8	32.4
(B) 40° eccentricity				
Left VF	321.7	38.3	270.7	24.7
Right VF	323.9	31.4	270.0	35.4
(C) 30° eccentricity				
Upper VF	406.3	30.6	295.2	36.6
Lower VF	400.7	23.9	287.5	36.6

n = 20 trials per condition. VF = visual field.

TABLE 4

	Conditions							
	40° 20° → ●		20° 40° ● ←		30° ↓ 10° ●		10° ● ↑ 30°	
(A) Correct responses (%, n = 40)								
Patient	65		60		55		58	
Normal subject	100		100		100		100	
(B) Motion detection time (in ms, n = 20) Mean (SD)								
Patient	1106.4	(129.4)	1045.8	(141.1)	990.0	(164.3)	967.1	(165.6)
Normal subject	365.6	(42.7)	371.5	(41.3)	374.4	(32.2)	378.2	(52.9)

A, percentage of correct responses of the patient and the normal subject (n = 40 trials per condition). B, mean detection time for both subjects (in ms, n = 20 trials per condition) for target movement in the outer visual field. The path of the moving target is indicated by the arrow. The black dots indicate the fixation point subject (t-test; $P < 0.001$). In addition, the patient's detection performance was at the most 65 per cent correct (out of 40 trials). In the peripheral visual field, the patient was never able to detect any direction of movement (i.e. towards the fixation point or away from the fixation point).

At this stage we thought it possible that the patient had difficulties with the discrimination task itself. In a control experiment we therefore presented either green (525 nm) or red coloured targets (650 nm) and, in a second condition, a circle- or a diamond-shaped target. All four targets had a diameter of 116 min of arc; luminance was 320 cd/m^2 (background luminance 3.2 cd/m^2). Targets were presented at 30 deg eccentricity along the left or right horizontal axis using the

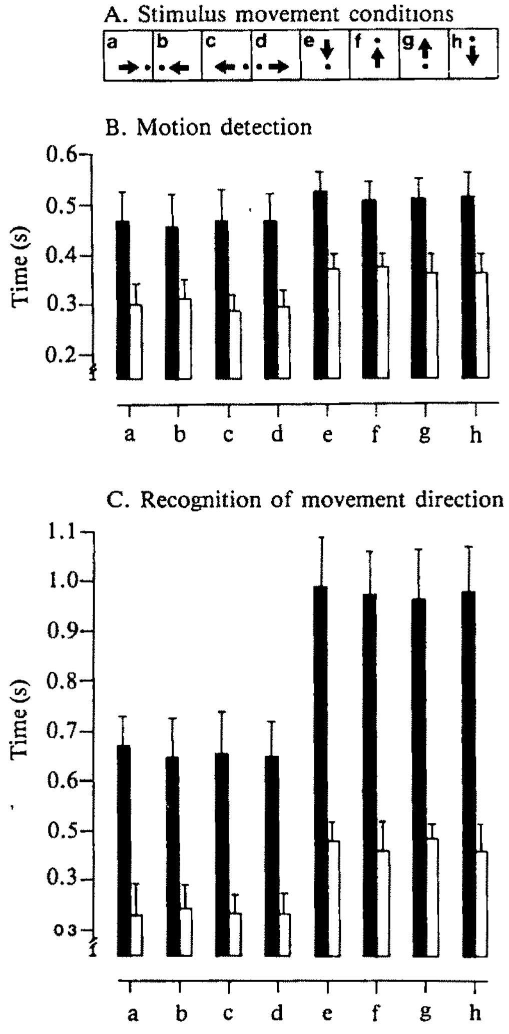

Fig. 7. Detection time for visual motion and direction of motion for the patient (black bars) and the normal subject (white bars). A, stimulus movement conditions a–h. The black dots indicate the fixation point, the arrow the direction of the moving light stimulus (from 15 deg eccentricity along the horizontal and vertical axes, respectively). B, mean time for motion detection in the different stimulus conditions. C, mean time for recognition of movement direction in the different stimulus conditions. Vertical bars indicate half standard errors (n = 20 trials per condition).

Tübingen perimeter. The patient had to press the buzzer-key whenever she could identify the colour or the form of the target. The relevant stimulus parameter (red or green; circle or diamond) was shown to her before testing. In addition, a white target of the same size and luminance was presented either stationary or moving at the same field position. The target was moved between 40 and 20 deg in both directions. In this condition the patient's task was to identify whether the target was in motion or was stationary. Presentation time was unlimited. Identification performance was measured in terms of time required for identification (Table 5). Mean identification time for colours and forms did not differ significantly (t-test, $P > 0.50$). However, the difference between the identification time for colours and forms and for the discrimination of a moving and a stationary light target was statistically significant (t-test, $P < 0.01$).

In a further experiment we presented two different forms (triangle and star) or two different colours (blue and yellow) tachistoscopically for 20 ms and increased the interstimulus interval until the patient was able to report the stimulus pair in the correct order of presentation. As judged from 5 trials each, a mean interstimulus interval of 33.8 ms (range: 33 to 38 ms) for the forms and 32.4 ms for the colours (range 30 to 35 ms) was sufficient for the patient to report the order of presentation correctly. The normal subject needed an interstimulus interval of 32.6 ms (28 to 34 ms) for the colours and 32.0 ms for the forms (31 to 34 ms). The difference in the interstimulus intervals between the two subjects is not statistically significant (t-test, $P > 0.10$).

TABLE 5 MEAN DISCRIMINATION TIME ($N = 10$, SD IN BRACKETS) BETWEEN TWO COLOURS, TWO FORMS AND BETWEEN A MOVING *VERSUS* A STATIONARY LIGHT TARGET

Conditions	*Patient*		*Normal subject*	
Red *versus* green	315.35	(55.7)	285.4	(25.0)
Diamond *versus* circle	306.10	(47.4)	295.7	(30.4)
Moving *versus* stationary target	998.6	(113.4)	274.7	(34.9)

The stimulus to be identified is underlined.

Motion prediction. In another experiment, the patient was asked to judge the velocity of a target moving horizontally over a path of 30 deg visual angle in front of her. Target diameter was 2 deg of arc at a viewing distance of 80 cm; its luminance was 30 cd/m^2 (background luminance: 2.2 cd/m^2). Velocity of the target was either 3, 6, 12 or 24 deg/s. An acoustic signal was presented and at the same time the target started to move. After the light square travelled a path of 10 deg (from left to right) it disappeared on the screen. At 30 deg, a white bar (5 x 2 deg) on the mask indicated the 'end' of the path. The patient pressed a key at the onset of the acoustic signal, and was asked to press the key again when she judged that the target, now invisible, had reached the white marker. Time was measured from the onset of the acoustic signal (which coincided with the beginning of the visual target's movement) to the instant the patient pressed the key again. This time was defined as the 'motion time' of the target, and served as a measure for the so-called motion prediction (Carlson, 1962). The same experiment was carried out with the normal subject. Both subjects were allowed to fixate the moving target, and to move their eyes and even their head across the mask. Ten trials were performed in each condition.

Fig. 8 shows the result in motion prediction for both subjects. Subjective stimulus velocity was calculated on the basis of mean prediction time for each condition. For the two 'lower' velocities (equivalent to 3 and 6 deg/s) the patient's judgements did not differ significantly from those of the normal subject (t-test, $P > 0.50$). For the velocities equivalent to 12 and 24 deg/s, however, the patient underestimated the speed of the target. The prediction time is significantly different between the two subjects for these two conditions (t-test, $P < 0.01$). It is interesting to note that for the condition with the highest velocity (24 deg/s) the patient commented that 'the target changed so rapidly its positions that I cannot respond accurately'. When forced to judge the time (after about 30 trials before testing) the patient's 'subjective velocity' was about 9 deg/s.

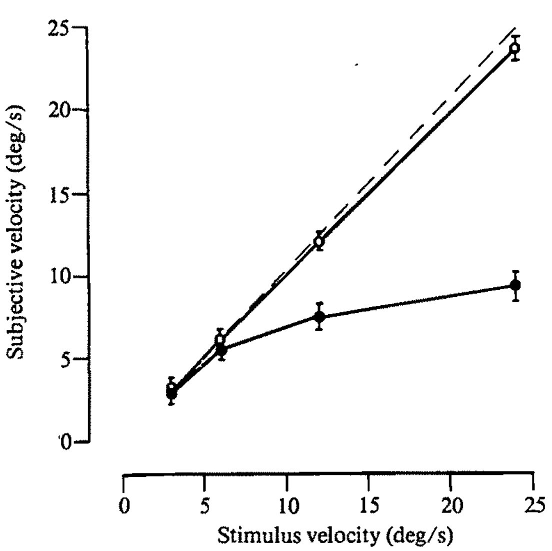

FIG. 8. Subjective velocity for the patient (closed circles) and the normal subject (open circles) as calculated from the motion prediction experiment (n = 10 trials per condition). Note the patient's underestimation of 12 and 24 deg/s stimulus velocity. Dashed line indicates perfect correspondence between stimulus and subjective velocity. Vertical bars. ±1 SD. For further details, *see text.*

Motion aftereffects. Two types of movement aftereffects were tested: aftereffects to vertical stripes moving in a horizontal direction (*see* Sekuler and Ganz, 1963), and to a rotating spiral (*see* Holland, 1957; Bakan and Mizusawa, 1963). A pattern of vertical black and white stripes (stimulus field 30 × 25 deg visual angle; stripe width 45 min of arc; contrast ratio bright to dark bars 1:13.6) was moved with a constant velocity of 6 deg/s horizontally from left to right. Viewing distance was 80 cm. After an inspection time of 30 s, the stripes were halted and the patient was asked to report whether or not she had any impression of pattern movement in the opposite direction. Throughout this test, fixation was maintained on a small dark circle in the centre of the stimulus field. Ten trials were conducted over two days; the time between successive trials was 5 min. The patient reported some kind of a motion aftereffects in only 3 of the 10 trials. Its duration, however, was rather short (1.2, 1.4 and 2.1 s) when compared with the normal subject tested under the same conditions (mean duration 6.7 s; 5 inspection periods). The patient described the motion after effect as an 'unrest' of the pattern, but never as movement.

For the spiral aftereffect, the stimulus disc (14 deg diameter at a viewing distance of 80 cm; black and white spiral width 1.2 deg visual angle) had a rotation speed of 15 r.p.m. (corresponding to a stimulus velocity of about 10 deg/s). The subject fixated a standard acorn nut which fastened the centre of the disc to the driveshaft. After an inspection time of 60 s the normal subject reported a clear aftereffect. The spiral appeared either expanding (when the disc was rotated clockwise), or shrinking (after anticlockwise rotation). The mean duration of the aftereffect (n = 5 trials in both directions) was 4.1 and 5.3 s. In contrast, the patient never reported any effect after inspection of the rotating spiral. In both motion aftereffect conditions the patient experienced the real movement of the pattern, but she never reported any impression of motion in depth of the spiral.

Apparent motion. The patient's ability to perceive apparent (*phi*) motion was tested under the same conditions as the perception of (real) horizontal motion. Two circular spots of light were each presented for a duration of 500 ms. The distance between the spots was varied from 2.5 to 15 deg, and the interstimulus interval was varied from 0 to 200 ms. Under no combination of conditions did the patient report apparent movement. She always reported two independent light spots. In contrast, the normal subject reported movement perception in conditions known to produce apparent motion (*see* Wertheimer, 1912; Korte, 1915).

Tactile and Acoustic Motion Perception

In order to discover whether the loss of movement perception was modality-specific, we tested the perception of movement by tactile and acoustic cues.

For *tactile movement* perception, the upper side of the patient's right forearm was stimulated by a small wooden stick (diameter 5 mm). The stick was moved either from the wrist towards the elbow or *vice versa*; motion path was about 10 cm. Pressure of the stimulus on the skin was rather low, but the patient reported always a clear sensation of contact. Stimulus velocity was either low (about 3 deg/s) or high (about 30 deg/s). The patient was asked to report whether she had perceived motion, and in which direction the stick was moved. She was seated on a chair, with her right arm on a table, and during the tests, she was blindfolded. The patient had no difficulty in performing these tasks; she made no error in 10 trials each. Responses were always given promptly.

Acoustic motion perception. A sound source was moved at a distance of 120 cm in a semicircle over a distance of 90 cm on either side, on a level with the ears. The continuous acoustic stimulus was produced by a siren (frequency range 300 to 1000 Hz; sound pressure 60 dB). The patient was again blindfolded, and seated on a chair. She was instructed to point to the position where she localized the sound source. Then the sound source was moved at a velocity of about 20 deg/s and the patient had to follow the sound source by finger pointing. She performed the task accurately and reported a clear motion of the siren by acoustic perception. When asked, she judged the direction of motion of the sound source with ease.

Pursuit Eye and Finger Movements

The effect of the disturbance of visual movement perception on visual-motor performance was examined by studying the pursuit movement of the eyes and of the index finger of the right hand. Pursuit eye movement performance was tested under visual conditions, whereas pursuit finger performance was tested under both visual and tactile conditions. Viewing condition was always binocular.

Pursuit eye movements. Stimulus conditions for testing pursuit eye movements were similar to those for testing horizontal movement perception (*see* p. 322). A circular light spot was moved in horizontal direction over a path of 30 deg in front of the patient. Target diameter subtended 0.5 deg visual angle at a viewing distance of 120 cm; target luminance was 14 cd/m^2 (background luminance 0.06 cd/m^2). Stimulus velocity ranged from 3 to 21 deg/s. The target was presented at eye level in front of the patient who was seated on a chair. She was asked to fixate and track the light target as accurately as possible. She was not allowed to make head movements. Eye movements were recorded from the lateral canthi using a DC system.

In fig. 9 pursuit eye movements are shown for a velocity of 4 deg/s (A) and 10 deg/s (B). From the recordings it is evident that the patient was able to follow the target quite accurately at the lower velocity. In contrast, when the target's velocity exceeded 8 deg/s, the eyes jumped from one turning point to the other (fig. 9C). Sometimes short periods of pursuit movement were observed; these periods disappeared totally, however, at a velocity of 12 deg/s. It is interesting to note that when the patient successfully tracked the target (i.e. up to about 8 deg/s), she always reported seeing movement.

It might be questioned whether the impairment in pursuit eye movements was due to an increased number of turnings (at the endpoints). In a control condition the target jumped between the two endpoints, and the patient was asked again to fixate the target. As would be expected for a normal subject, the patient made saccades

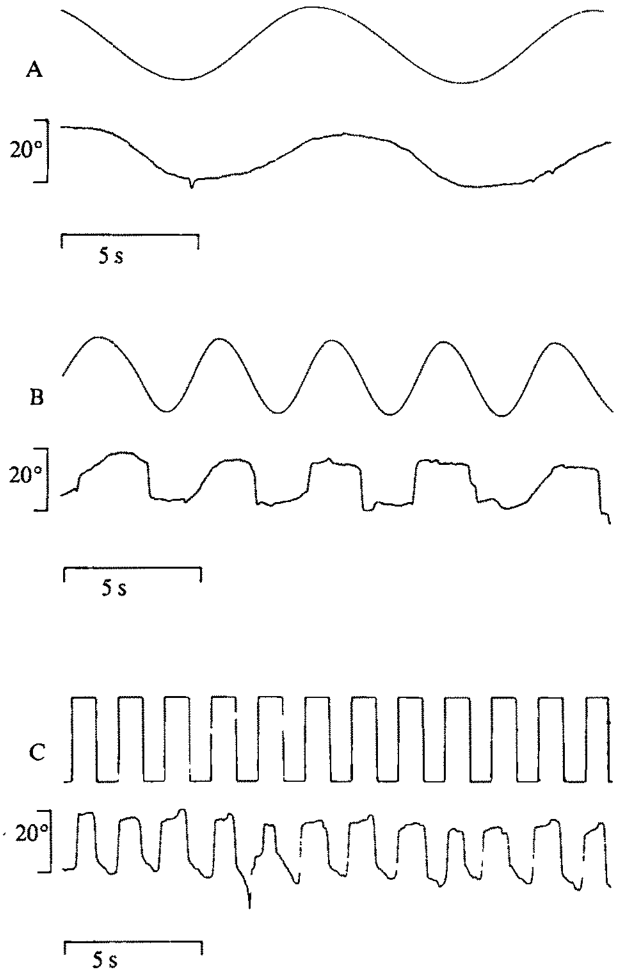

FIG. 9. Electro-oculographic recordings of the patient's pursuit eye movement to a target moving either at 4 deg/s (A) or at 8 deg/s (B) In C the saccadic responses to a target 'jumping' at 1 Hz are shown. For further details, *see text.*

between the endpoints. However, even at a frequency of 1/s, she had no difficulty in performing this task.

Pursuit movements of the finger. Finger pursuit movement was tested by using a wire as stimulus path. The wire was mounted on a board (94 × 28 cm), and had a diameter of 2 mm. The patient's task was to follow the path of the wire from left to right with the index finger of the right hand. Three different stimulus conditions were used: (A) a straight line (i.e. without change in direction), (B) a saw-tooth line, and (C) a line with irregular changes in direction (*see* fig. 10, *top*). The length was either 88 cm (A), 118 cm (B) or 245 cm (C). The patient was seated in a chair in front of the board, and she was instructed to move her finger along the path of the wire as fast as possible but without leaving the wire. Pursuit movement performance was tested under tactile, tactile-visual and visual conditions. In the tactile condition, the patient was blindfolded, whereas in the visual condition a sheet of glass was put over the board so that no tactile information about the path of the wire was available. In the combined conditions the patient had access to both tactile and visual information. In this and in the visual condition, the viewing distance was about 40 cm. The patient was allowed to make eye and head movements. Performance was judged in terms of time per trial. Before testing, the patient performed about 50 trials in order to overcome learning effects occurring in the first sessions. The normal subject was tested under the same conditions.

Fig. 10 (B) (*bottom*) shows the results for the various conditions. The patient had no difficulty in moving her right index finger along the various tactile 'paths'; in particular she never made any returns, i.e. retracings. The patient performed best in the tactile condition and very poorly in the visual condition. The difference is highly significant (t-test, $P < 0.01$). In contrast, the normal subject performed significantly better in the visual than in the tactile condition (t-test, $P > 0.02$). Furthermore, the patient did not benefit from the visual information in the tactual-visual condition (as compared with the tactile condition; t-test, $P > 0.20$), whereas the normal subject performed significantly faster in the 'mixed' as compared with the tactile condition (t-test, $P < 0.01$). In the visual-tactile condition, the normal subject was even better than in the visual condition (t-test, $P < 0.01$). The patient herself commented on her poor performance in the visual condition and reported that the difficulty was 'between my finger and my eyes. I cannot follow my finger with my eyes if I move the finger too fast'.

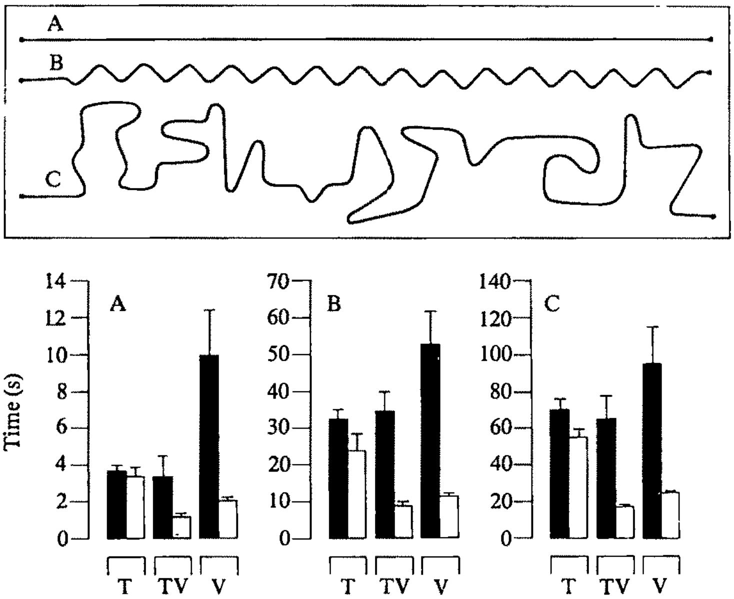

FIG. 10 Pursuit finger movement time of the patient (black bars) and the normal subject (white bars) along a wire of different length and course (A–C) under tactile (T), visual (V) and tactile-visual (TV) conditions. Vertical bars indicate half range. Note the increased movement time of the patient under the visual condition For further description *see text*

DISCUSSION

It seems evident that our patient suffered a disturbance in movement vision. This disturbance was highly selective since other visual functions did not reveal any essential disorder, neither was a visual field defect found, nor were field regions amblyopic, as often described in patients with cerebral damage (Poppelreuter, 1917; Polyak, 1957; Teuber *et al.*, 1960). Detection performance and localization accuracy were not impaired. In addition, the visual field for coloured targets was not contracted as found in patients with damage to the occipitotemporal cortex (Henschen, 1890). It remains to note, however, that stereoacuity was rather low (120 s of arc) when compared with the normal subject (30 s of arc).

The increase in visual reaction time (as compared with the normal subject) may be interpreted as an unspecific sign of brain damage (*see* Blackburn and Benton, 1955). Furthermore, the disorder in movement vision cannot be attributed to an impairment in 'temporal acuity'. This temporal resolving power in the visual sense has been considered as the minimum time interval that can separate two visual events (that is, critical flicker fusion (CFF)), and as the perceptual experience of temporal order (Hirsch and Sherrick, 1961). The patient's CFF values were not diminished, neither foveally nor in the periphery of the visual field. In addition, the temporal separation required to report two different colours or forms in the correct order of their presentation was not increased significantly when compared with the normal subject. These main 'temporal processing units' (Pöppel, 1978) were therefore not impaired in our patient.

The patient's disturbance in movement vision can be characterized as follows. Movement vision in depth was completely abolished. For visual targets moving along the horizontal or vertical axes in the inner visual field (that is, up to about 15 deg eccentricity), movement perception was somewhat preserved. In this field region the patient could distinguish between different directions of movement, and could also judge fairly accurately the velocity of the target provided that it was below 10 deg/s. In contrast, in the periphery of the visual field the patient's movement sensitivity was restricted to the discrimination between a moving and a stationary target.

Since the patient performed quite accurately when the target was presented in the inner visual field, or when she could fixate and track the target, the disturbance in movement vision cannot be attributed to a difficulty in understanding or performing the task itself. However, it is interesting that the patient's difficulty in detecting the direction of the moving target could not be reduced by her knowledge of the particular direction of movement before testing, as is found in normals (Sekuler and Ball, 1977).

Movement vision for targets travelling along the horizontal plane was somewhat better than for targets moving along the vertical plane. This difference, however, was also found for the normal subject, and is in agreement with observations reported by other authors (*see* Choudhury and Crossey, 1981), indicating that movement sensitivity (at least for low movement speeds) in the human field of vision differs for the two main axes.

The dissociation between movement sensitivity in the outer and in the inner visual fields may be due to a lower sensitivity for slowly moving targets in the periphery as compared to the centre of the visual fields (Tynan and Sekuler, 1982). Alternatively, however, the nearly complete loss of movement vision beyond 15 deg eccentricity may be interpreted in terms of a 'bilateral hemianopia' for moving targets with retention of the central visual field for movement vision. This interpretation is supported by the observation that the patient never experienced any movement vision in the periphery.

In addition, sensorimotor capacities that depend on movement vision were also affected. Performance of pursuit eye movement mirrored quite clearly the perceptual disorder with respect to the speed of the moving target. A similar picture emerged from testing pursuit finger movements. In the visual condition the patient required more than twice the time as compared to the tactile condition, probably due to the diminished sensitivity for target velocity (in this condition her finger served as moving target).

The disorder in movement perception was restricted to the visual modality. Acoustic and tactile movement perception were not found to be impaired. Interestingly, the patient did not show any visual motion after effects, nor did she possess apparent (*phi*) visual movement perception.

The reports by Pötzl and Redlich (1911) and by Goldstein and Gelb (1918), together with the observations in our case, may be taken as evidence that movement vision can be disturbed selectively after circumscribed cerebral damage. Goldstein and Gelb (1918) interpreted the disorder in movement vision in their patient as a 'special form of apperceptive psychic blindness'; other authors favoured the idea of a rather distinct neural mechanism beyond the striate cortex underlying the perception of movement (Best, 1919; Poppelreuter, 1923). This idea was repudiated by Bender and Teuber (1949) who argued from their observations that there is a 'unitary physiologic factor' underlying the perception of flicker, apparent motion and real motion. According to this hypothesis, disturbance in movement vision *cannot* occur without a reduction in critical flicker fusion. Furthermore, Teuber (1960) has pointed out that after cerebral damage, movement vision is always affected together with form perception, but never selectively. The observed association and dissociation of visual symptoms after cerebral damage simply illustrates an order of different 'vulnerability' of visual functions rather than a selective impairment (Teuber *et al.*, 1960). The observations obtained in our patient are incompatible with this concept, since fusion of visual flicker, and form and colour vision were not impaired.

One can only speculate about the critical site and, perhaps, the extent of the cortical damage responsible for the impairment in movement vision. In both cases reported in the literature (Pötzl and Redlich, 1911; Goldstein and Gelb, 1918) there is evidence only that the patients suffered bilateral damage to the posterior brain.

The patient of Pötzl and Redlich (1911) suffered most probably a bilateral infarction in the territory of the posterior cerebral artery. The gunshot injury sustained by the patient of Goldstein and Gelb (1918) occurred, according to the authors, in the lateral and medial parts of the left occipital lobe. The bilateral homonymous visual field loss, however, indicates that the posterior brain was damaged on both sides. The presence of an anomic aphasia in both cases indicates that the lesion was not restricted to the occipital lobe. Since no autopsy findings are available nothing conclusive can be said about the precise site and extent of the brain lesion in these two patients.

On the basis of the CT findings and the results of neuropsychological testing it can be concluded that in our patient most of the parietal cortex (areas 39, 40, 7) and the relevant afferents were spared or only partially damaged, since no neuropsychological deficit known to result from damage to the angular and supramarginal gyri and the posterior parietal cortex (*see*, for example, LeDoux, 1979) was prominent. It may be suggested, therefore, that the disorder in movement vision is due to the bilateral lesion affecting the lateral temporo-occipital cortex, namely, the posterior part of the middle temporal gyrus and the lateral occipital gyri. Even though it remains speculative, it could be hypothesized that these regions are homologous to those cortical areas in the monkey which have been found to contain movement-sensitive cells in heavy concentrations. In the monkey, it seems that especially the areas around the posterior third of the superior temporal sulcus play an important role in the analysis of visual stimulus movement. Neurons in this cortical region were found to respond to stimuli moving at velocities from 5 deg/s up to 50 deg/s. The majority are directionally selective and many of these prefer motion in depth (e.g. Zeki, 1974). The superior temporal sulcus receives connections from other visual areas in the striate and prestriate cortex; these connections were found to be topographically organized and are reciprocal (Zeki, 1974; Rockland and Pandya, 1981). Ungerleider and Mishkin (1979) were able to show that the caudal portion of the superior temporal sulcus receives a direct projection from the striate cortex representing the central visual field and also from areas of the striate cortex representing peripheral vision. This portion of the superior temporal sulcus contains a map of the entire contralateral visual field similar to that found in the striate cortex. Receptive fields at a given eccentricity are, however, much larger and topography is cruder than in the striate cortex (Zeki, 1974; Gattass and Gross, 1981).

An alternative explanation for the observed selective visual disorder is a disconnection of the cortical area in question from the striate cortex. As pointed out earlier (p. 315 and fig. 1), the temporal, parietal and occipital white matter was markedly damaged bilaterally. It is therefore plausible that the deafferentation of the cortical area responsible for the visual perception of movement resulted in the observed disturbance in our patient.

The effect of disturbed movement vision on eye and finger tracking under visual control becomes plausible if it is assumed that the sensorimotor cortical region functionally related to the visual area concerned with the analysis of movement no longer receives visual input from this sensory area. Parietal area 7 was found to contain directionally selective 'visual tracking' neurons, which are activated during foveal fixation of a moving target (Hyvärinen and Poranen, 1974; Lynch *et al.*, 1977; Robinson *et al.*, 1978; Sakata *et al.*, 1980). Hyvärinen and Poranen (1974) also described neurons in area 7 which were activated by hand tracking movements including eye fixation of the moving stimulus to be tracked with the hand.

Area 7 was certainly not damaged in our patient. The impairment in pursuit eye and finger movement may again be due either to the destruction of the visual area in question or because area 7 has been disconnected from this visual area. In the monkey, none of the visual areas has been found hitherto to project directly to area 7. The visual input to this parietal region is probably relayed indirectly through the corticocortical route from the circumstriate belt (Pandya and Vignolo, 1969) and from the superior temporal gyrus (Spatz and Tigges, 1972). The white matter lesion in our patient could well have destroyed parts of this pathway.

In conclusion, the observations obtained in our patient indicate that selective disturbance of movement vision can occur after circumscribed bilateral cerebral damage. The observed visual disorder may be taken as evidence that movement vision may be considered as a 'special visual perception' (Riddoch, 1917; Gibson, 1968). Psychophysical experiments showing selective adaptation effects on visual movement sensitivity, that is, for direction and velocity (Pantle and Sekuler, 1968, 1969; Ritter *et al.*, 1973) support this hypothesis. The loss of visual movement aftereffects and of visual apparent (*phi*) movement in our patient indicate that the same perceptual mechanism probably underlies vision of 'real' and apparent movement and of movement aftereffects irrespective of differing stimulus conditions (Wertheimer, 1912; Gibson, 1954, 1968).

The selectivity of the visual disturbance in our patient also supports the idea of a functional heterogeneity of those cortical areas which are responsible for the processing of the various dimensions of the visual surroundings. On the basis of observations of selective visual disorders in brain-damaged patients it can be suggested that the visual cortex in man is specialized in the way that has been described in the monkey (Zeki, 1978). The existence of highly specific disorders in vision suggests that some degree of parallel processing in different cortical areas occurs in the human visual cortex (Cowey, 1979, 1982). But, as Campbell pointed out in 1905, 'Definite confirmation or refutation of this point (i.e. the precise differential localisation of function) will not be forthcoming until the positive and negative facts adduced from the careful analysis and digestion of many more cases are weighed and sifted.' Since cases with a highly selective visual disorder seem to be rare, the detailed testing of a single patient can tell us much more than group studies of patients with multiple defects that are difficult to compare (Shallice, 1977; Cowey, 1982).

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SUBCORTICAL SOMATOSENSORY EVOKED POTENTIALS TO MEDIAN NERVE STIMULATION

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SUMMARY

1. Somatosensory evoked potentials to median nerve stimulation recorded from neck-scalp derivation consisted of four components: two negativities (N10 and N12) which were recorded from the neck electrode and two positivities (P11 and P13) which were recorded from the scalp electrode.

2. Evidence is presented pointing to the following origin of these components: N10 = afferent volley at the peripheral nerve immediately before it enters the intervertebral foramen; P11 = afferent volley at the dorsal rootlets of C6; N12 = postsynaptic dorsal cord potentials (ipsilateral dorsal horns of C6, C7); P13 = afferent volley in dorsal column at the level of the foramen magnum.

3. In the neck-scalp derivation the two main upward deflections are best identified by using a low cervical recording electrode and filtering out slow components of less than 150 Hz. Applying this technique the two main upward deflections can be consistently identified in all controls and correspond exactly to the latencies of peaks P11 and P13. The cervical components N10 and N12 are obscured by the more prominent positivities from the scalp.

4. Evidence is presented which suggest that the three far field potentials recorded from Fpz are due to the abrupt change in current flow produced when the afferent volley enters the cervicothoracic muscle groups at the axilla (P8), the spinal canal (P11) and finally the skull (P13).

5. The fact is stressed that in recording far field potentials, both recording electrodes (grid I and grid II) are usually active. Proof is presented that even the frequently used contralateral shoulder or hand noncephalic reference picks up a triphasic wave which reflects the afferent volley as it passes through the neck.

6. No evidence was obtained that the ascending volley in the cervical dorsal columns ('traveling wave') contributes to any significant degree to the potentials recorded from cervical electrodes.

7. For routine recordings of subcortical somatosensory evoked potentials the following procedures are recommended.

(a) Low cervical-midfrontal montage complemented by noncephalic 'reference' recording (low neck-contralateral shoulder and midfrontal-contralateral shoulder).

(b) Filtering out of slow frequencies under 150 Hz for selective recording of the afferent volley. This can be complemented by open low frequency filter settings to amplify selectively the dorsal cord potential (N12).

(c) Measurement of relative latencies with respect to the negative peak recorded at the clavicle (P11-N9; P13-N9; P20-N9).

(d) Transformation of amplitudes into logarithms for statistical analysis and the use of logarithms of ratio of amplitudes (left/right and unilateral/bilateral) to define abnormalities of amplitudes.

INTRODUCTION

Subcortical somatosensory evoked potentials to median nerve stimulation are used in many laboratories as routine tests of functional integrity of the afferent somatosensory pathways. Techniques for recording these potentials vary between laboratories but can be subdivided into two main groups: laboratories that use the *scalp to noncephalic reference* montage (Cracco and Cracco, 1976; Anziska *et al.*, 1978; Kritchevsky and Wiederholt, 1978; Shimoji *et al.*, 1978; Arezzo *et al.*, 1979; Green and McLeod, 1979; Cracco *et al.*, 1980; Desmedt and Cheron, 1980; Grisolia and Wiederholdt, 1980; Yamada *et al.*, 1980) and those that use *neck to scalp montages* (Matthews *et al.*, 1974; Mastaglia *et al.*, 1976; Small and Jones, 1977; Colon *et al.*, 1977; Jones, 1977; Hume and Cant, 1978; El-Negamy and Sedgwick, 1979; Hallet, 1979; Lehman *et al.*, 1979; Lesser *et al.*, 1979; Pratt *et al.*, 1980; Abbruzzese *et al.*, 1980; Chiappa *et al.*, 1980; Ganes, 1980; Obeso, 1980; Spudis *et al.*, 1980; Strenge *et al.*, 1980).

Three main positivities are described in the scalp-noncephalic reference montage and at least two clearly defined upward deflections in the neck-scalp derivations. These peaks are used in clinical tests to identify and to localize lesions of the afferent somatosensory pathways. There is still, however, significant controversy regarding the generators of these peaks, limiting greatly the interpretation of these clinical tests.

This paper attempts to solve some of the controversies by careful analysis of neck-scalp and scalp-noncephalic reference montages in a control group. This is complemented by comparing the potentials recorded on surface montages with intrasurgical tracings obtained while monitoring evoked potentials.

METHODS

The median nerves were stimulated unilaterally and bilaterally at the wrist with the positive electrode placed on the dorsal wrist and the negative electrode on the volar wrist directly over the median nerve. With the stimulator set at a constant supramotor threshold current the position of the negative electrode which produced the maximum twitch of the thumb was determined. The stimulus was delivered using Grass 9 mm disc electrodes. The disc electrodes were applied with collodion and the resistances were reduced to less than 5000 ohms by filling them with Medi-trace EKG solution and then gently abrading the skin. The stimulus was a constant current square wave delivered by a Grass S88 stimulator by way of a Grass SIU5 stimulus isolation unit. For averaging, the stimulus intensity equalled motor plus sensory threshold (the intensity of the motor threshold and sensory thresholds were determined and the stimulus intensity set at the algebraic sum of these two intensities) (Lesser *et al.*, 1979). The stimulus had a duration of 0.3 ms and a regular repetition rate of 2 to 5 Hz; 400 to 1000 responses were averaged. The upper limb skin temperatures varied between 31 and 35° C (average 32.7°) during the experimental sessions. Recordings were obtained using Nicolet HGA-200A amplifiers. Averaging was accomplished with a Nicolet NIC-80 averager with a 12 bit analog to digital conversion. The dwell time varied between 10 and 42 μs and the analysis time between 40 and 84 ms. The standard filter settings were 150 to 1500 Hz (-3 dB). In selected studies special filter settings of 30 to 1500 Hz, 1 to 1500 Hz, 1 to 250 Hz and 1 to 100 Hz were used. The responses were stored on flexible discs by means of a Nicolet 299 storage unit and then plotted with a Hewlett Packard model 7010B X-Y recorder. The ongoing EEG activity was monitored with a Tektronix 5110 four channel oscilloscope and responses contaminated with muscle artefact were rejected by the computer operator. In addition, the amplitude of each individual trial was evaluated by the averaging program and trials which exceeded a threshold voltage preset by the computer operator on the basis of the amplitude of artefact were automatically rejected by the computer. Up to 16 channels were recorded simultaneously.

The recording electrodes consisted of Grass 9 mm disc electrodes which were applied in the same way as the stimulating electrodes. Recordings were obtained from the following positions:

Foot = foot contralateral to stimulation side
Hand = dorsal hand contralateral to stimulation side
Ax = axilla ipsilateral to stimulation side
Cl = midpoint of clavicle ipsilateral to stimulation side
Cl_1 = midpoint of left clavicle
Cl_2 = midpoint of right clavicle
Sh_2 = right shoulder
SC_7 = skin surface electrode over C7 spinous process
SC_6 = skin surface electrode over C6 spinous process
SC_5 = skin surface electrode over C5 spinous process
SC_4 = skin surface electrode over C4 spinous process
SC_3 = skin surface electrode over C3 spinous process
SC_1 = skin surface electrode over C1 spinous process
A_1 = international 10-20 system A_1 (left ear)
A_2 = international 10-20 system A_2 (right ear)
Fpz = international 10-20 system Fpz (midfrontopolar)
Fz = international 10-20 system Fz (midfrontal)
C_4 = international 10-20 system C_4 (right central).

Intraoperatively, electrodes were placed for monitoring purposes on the dura above the level that was manipulated surgically. A Grass needle electrode placed in the skin at approximately the level of the operation served as reference. Multiple electrodes were placed to ensure the adequacy of the monitoring and to avoid the possibility of a technical failure in a single electrode or channel. The rationale for this procedure has been reported separately (Lueders, Gurd, Hahn *et al.*, 1982; Hahn *et al.*, 1981).

Data were obtained from repeated experiments on 20 normal subjects (13 female and 7 male; aged 20 to 40 years, average 29.9 years), all of whom had given informed consent to the experimental procedures. The recordings were obtained during sleep, either spontaneous or induced with 5 to 10 mg diazepam orally.

The following nomenclature is used for identification of peaks in this paper. Peaks are labelled either N or P depending on whether they are generated mainly as a negativity or positivity (Lesser *et al.*, 1979; Lueders, Andrish, Gurd *et al.*, 1981; Lesser *et al.*, 1981; Lueders *et al.*, 1983). 'Negativity-up' convention was used in all recordings. The number following N or P corresponds to the average latency of that peak in normal controls (Donchin *et al.*, 1977). For example, labelling an upward deflection at SC_5-Fpz as P13 would indicate that it is generated mainly as a positivity from Fpz and that the average latency of that peak in normal controls was approximately 13 ms. On the other hand labelling it as N13 would indicate that it is generated mainly as a negativity from SC_5.

RESULTS

Standard Recording Technique

Fig. 1 shows our standard recording technique for recording early somatosensory evoked potentials to median nerve stimulation. In the first channel there is an initial triphasic potential (low amplitude downward deflection, high amplitude upward deflection labelled N9, medium amplitude downward deflection) followed by longer latency, relatively lower amplitude undulations. There is general agreement that the initial triphasic potential is the reflection of the afferent volley as it passes through the brachial plexus immediately beneath the electrode placed on the clavicle. The major upward deflection is labelled N9 because it is recorded as a negativity from grid I and in normal controls has an average latency to left and right stimulation of 9.2 and 9.4 ms, respectively (*see* Table). The undulations following the initial triphasic wave closely resemble the recording obtained in channel 2 (difference of amplitude is due to different amplification factors); evidence indicating that these potentials are mainly recorded from Fpz (grid II) will be presented below.

In the second channel (neck-scalp derivation) there are two major upward deflections which are labelled P11 and P13. These upward deflections are labelled P because they are recorded *mainly* as positivities from grid II, namely, Fpz (*see* evidence below). It is important to stress, however, that negative potentials picked up at the neck electrode also contribute to the generation of these two upward deflections. They had average latencies of 11.2 to 11.4 and 12.3 to 12.5 ms in our control studies. P13 is followed by a major downward deflection (N15) which is

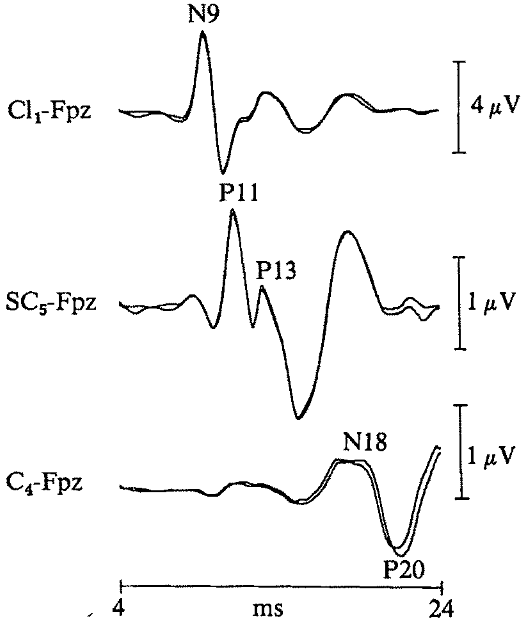

FIG. 1 Somatosensory evoked potentials to left median nerve stimulation. Filters. 150 to 1500 Hz (−3 dB in this and following figures). Number of stimuli: 800. For abbreviation of montage in this and following figures *see* Methods.

recorded as a negativity from Fpz (*see* evidence below) and had a latency of 14.8 to 14.9 ms in our control studies (*see* Table). This negativity clearly precedes the first cortical component N18 shown in the third channel.

In the third channel there are prominent upward-downward deflections labelled N18 and P20, respectively. Evidence that both these potentials are recorded from C_4 has been presented in another paper (Lueders *et al.*, 1983). These potentials had average latencies of approximately 18.2 to 18.3 and 20.1 to 20.3 ms in our control studies (*see* Table).

TABLE. NORMAL LATENCIES AND AMPLITUDES

LATENCIES (ms)

Component	N9	P11	P13	N15	N18	P20
Left stimulation	9.20+0.51	11.18+0.65	12.27+0.81	14.81+0.72	18.15+0.77	20.11−0.83
Right stimulation	9.38+0.53	11.35+0.70	12.49+0.62	14.94+0.78	18.29+0.96	20.32+0.85
Left-right	−0.19+0.20	−0.18+0.29	−0.23+0.51	−0.14+0.44	−0.32+0.50	−0.12+0.66

LATENCY DIFFERENCES (ms)

Component	P11-N9	P13-N9	P20-P13	P20-N9
Left stimulation	1.97+0.26	3.06+0.52	7.82+0.63	10.95+0.63
Right stimulation	1.96+0.30	3.10+0.39	7.83+0.62	10.97+0.67
Left-right	0.01+0.25	0.04+0.47	−0.05+0.71	−0.02+0.57

AMPLITUDE (LOG μV)

Component	P13
Left stimulation	0.87+0.31
Right stimulation	0.76+0.28
Left-right	0.11+0.25

Normal Latencies and Amplitudes

The Table shows the latency differences P11-N9, P13-N9 and P20-N9. The latencies of the peaks P11, P13 and P20 are expressed in relative terms (latency differences with respect to N9) to correct for the effect produced by different arm lengths and different temperatures of peripheral nerves. This method will also correct for significant differences between left and right arm lengths. The latency differences have consistently smaller standard deviations than the corresponding absolute latencies. This is almost certainly due to the standardization introduced by eliminating variation in arm length. When evaluating interpeak latency (P11-N9 or P13-N9) the variability of left minus right median nerve stimulation was significantly less than the absolute interpeak latency differences. For example, for P13-N9 values of 1.54 ms and of 4.27 ms are within average ± 3 standard derivations. A right-left interpeak latency difference of more than 1.41 ms, however, falls outside that range.

No significant correlation was found between latency differences P11-N9 or P13-N9 and arm length and/or distance between the clavicle and C_5 vertebral spine electrodes.

Peaks P11 and P13 were identifiable in all 20 controls to independent left and right median nerve stimulation (average of 400 stimuli). In 10/40 tracings P13 was higher

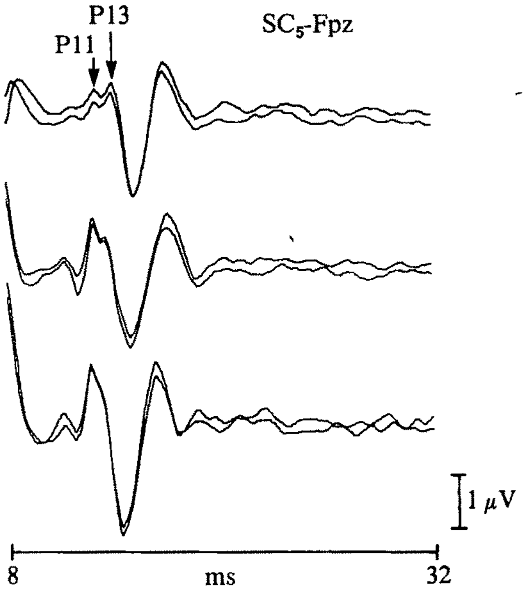

FIG. 2. Variability of potentials recorded at neck-scalp derivation to median nerve stimulation in three different subjects. Filters: 150 to 1500 Hz.

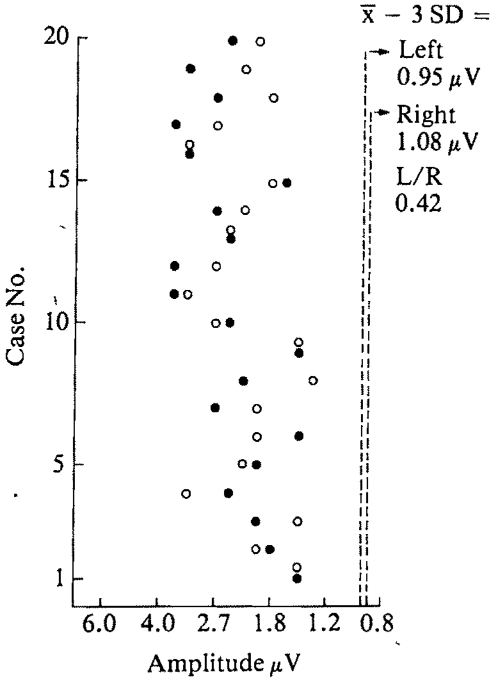

FIG. 3. Amplitude of peak P13 (measured as difference between peak P13 and N15). Broken line on the right side shows the upper limit of normality set arbitrarily at X̄ – 3 SD. X-axis is a logarithmic scale of the amplitude in μV. n = 20. Filled circles = left arm Open circles = right arm

than P11 and in 19/40 tracings P11 was higher than P13. In 11/40 tracings the two peaks were of approximately the same height. In 3/40 tracings P13 was only identifiable as a shoulder of the downward slope from P11 (fig. 2). Fig. 3 shows the interindividual variability of the amplitude P13 (amplitude difference between peaks P13 and the following deflection N15). The amplitude is expressed as a logarithm because in a previous study we demonstrated that the amplitude of the cortical SEPs had an approximately normal distribution when expressed logarithmically (Lueders, 1970). Using a logarithmic distribution, the boundaries of normality (defined as average ± 3 SD) cover all the normal controls and have a lower limit of normality of approximately 1 μV. The equivalent values when absolute amplitudes are used are the following: left side stimulation: 2.49 ± 0.75 μV (average 3 SD = 0.24 μV); right side stimulation: 2.20 ± 0.61 μV (average 3 SD = 0.37 μV). In other words, the lower limit of normality would become so small that amplitude could not be used for clinical evaluation of abnormality. It should be emphasized that these amplitude measurements are a function of the bandpass used for recording in this study (150 to 1500 Hz) and that a different bandpass for the standard recording will give different values.

Bilateral and Unilateral Stimulation

Fig. 4 illustrates the fact that bilateral stimulation produced significantly higher amplitude responses, approximately the sum of the unilateral potentials. The latency of the potentials did not change. The results obtained in comparing unilateral and bilateral stimulation in 20 controls are shown in fig. 5. As expected, the average amplitude ratio is 0.5 and all normal controls are contained within ± 3 SD (amplitude expressed as logarithm). The limits of normality indicates that unilateral amplitudes should always be less than 0.8 to 0.9 the bilateral amplitude.

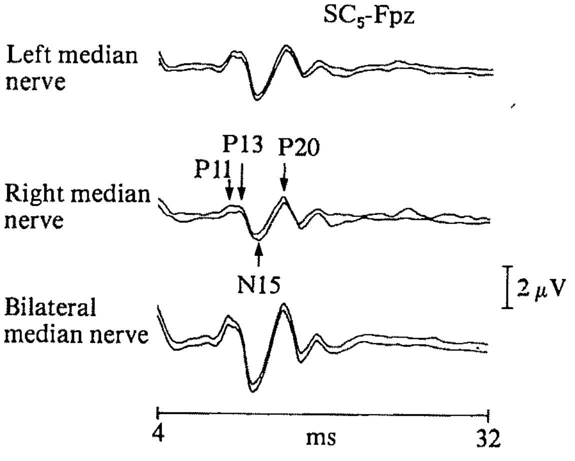

FIG. 4. Comparison of somatosensory evoked potentials recorded at neck-scalp derivation to left, right and bilateral median nerve stimulation. Filters. 150 to 1500 Hz

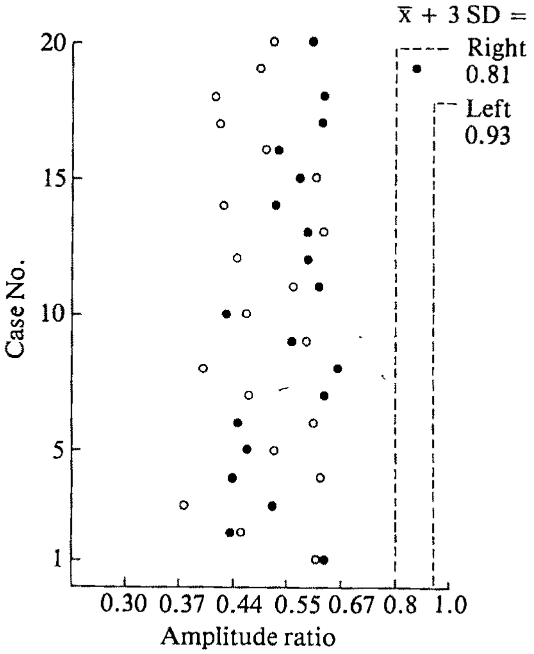

FIG 5. Ratio of amplitude of P13 somatosensory evoked potentials to unilateral and bilateral stimulation In the X-axis the ratio is expressed in logarithms. The broken line on the right side shows the upper limit of the ratio set arbitrarily at X̄ ± 3 SD

Effect of Filters

Increasing the band width of the low frequency (LF) filters from 150 to 30 Hz or 1 Hz produced only a slight increase in amplitude of P11 (approximately 40 per cent) and the main increase was seen when the LF filters were opened from 150 to 30 Hz (fig. 6). Conversely, P13 increased greatly (approximately 140 per cent) and progressively as the LF filters were opened to 30 Hz and then to 1 Hz. P11 was higher in amplitude than P13 when the low frequencies were filtered out, but with LF filters of 1 Hz, P11 appeared only as a shoulder in the upward slope toward P13.

Filtering out the high frequencies had an even more dramatic effect (fig. 6). At a high frequency (HF) setting of 250 Hz, P11 disappeared almost completely whereas there was little effect on the amplitude of P13. With an HF filter setting of 100 Hz, P13 also started to decrease greatly in amplitude. Notice also that the different filter settings had almost no effect on the latency of P11. The latency of P13, however, increased slightly by opening the low frequencies and markedly by reducing the higher frequencies.

Thus P11 and P13 are composed of clearly differentiable frequency components: P11 consists mainly of frequencies above 250 Hz and P13 mainly of frequencies below 250 Hz. Fig. 7 shows that P11 can be isolated more easily when frequencies below 150 Hz are filtered out. Recordings in which low frequencies are filtered out usually have a significantly lower amount of noise and, therefore, relatively greater amplification factors can be used.

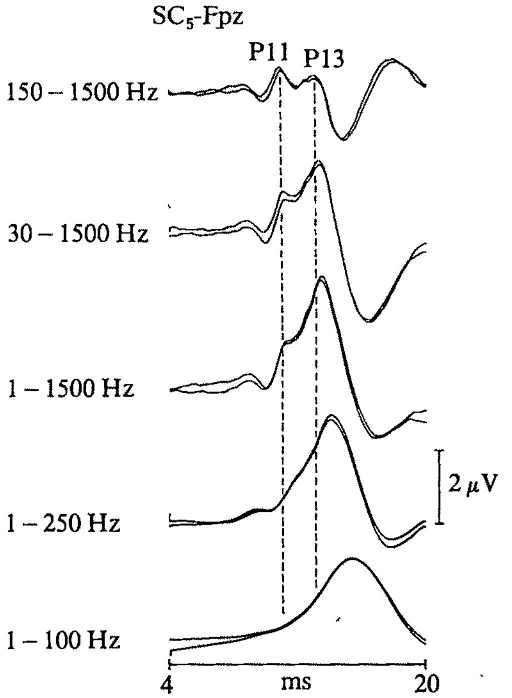

FIG. 6. Effect of filter settings on waveform and amplitude of evoked potentials to left median nerve stimulation recorded from neck-scalp derivation (SC_5-Fpz).

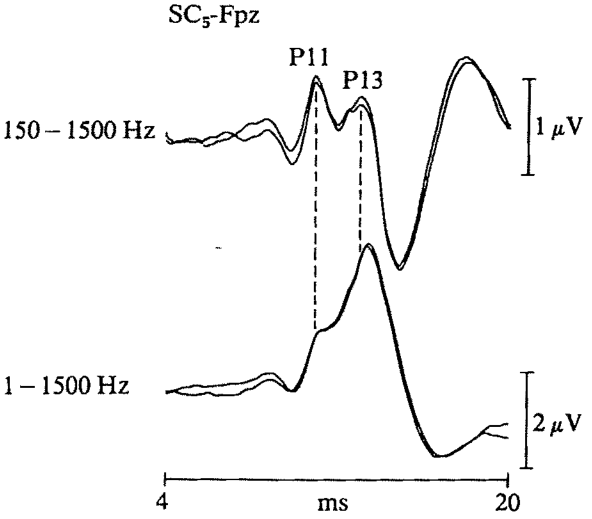

FIG. 7. Effect of filter settings on waveform of evoked potentials to left median nerve stimulation recorded from neck-scalp derivation (SC_5-Fpz)

Afferent Volley in Shoulder and Neck

To elucidate the origin of the potentials recorded fron neck-scalp derivations, electrodes were placed on the surface along the afferent pathways from the median nerve (grid I) and all the recordings were made with Fz in grid II (fig. 8). P13 (dotted line) is of the same latency (12.6 ms) and points upwards in all derivations. This indicates that P13 is most probably picked up by Fz as a positive peak. The progressively lower amplitude of P13 at the high cervical level is most probably a cancellation effect.

Following P13 there is a downward deflection (N15) which like P13 has the same latency in all derivations. N15, however, does not decrease in amplitude at the high cervical level. This peak is most probably picked up by Fz as a negativity.

Preceding P13 there is an upward peak which shows progressively longer latencies between axilla (7.3 ms) and SC_5 (10.9 ms) and almost disappears at the SC_2 derivation. This potential, of progressively longer latency between the axilla and SC_5, is a direct reflection of the afferent volley in the peripheral nervous system and, therefore, is a negative peak recorded from grid I. At SC_5 this peak corresponds to P11 which will be analysed in more detail below.

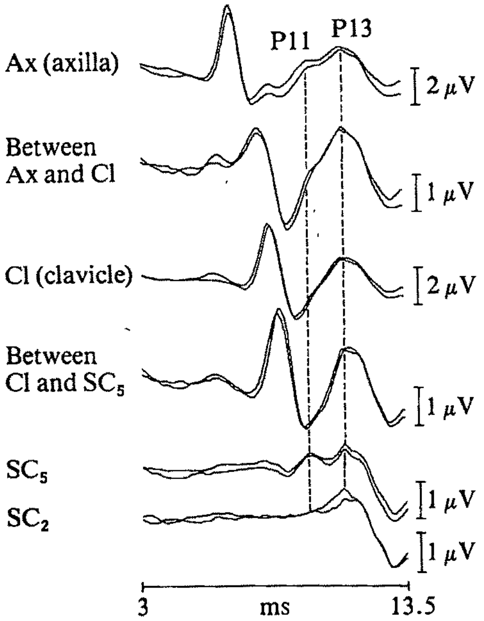

FIG. 8. Somatosensory evoked potentials recorded from shoulder and neck with Fz reference. Stimulation· left median nerve. Filters· 150 to 1500 Hz.

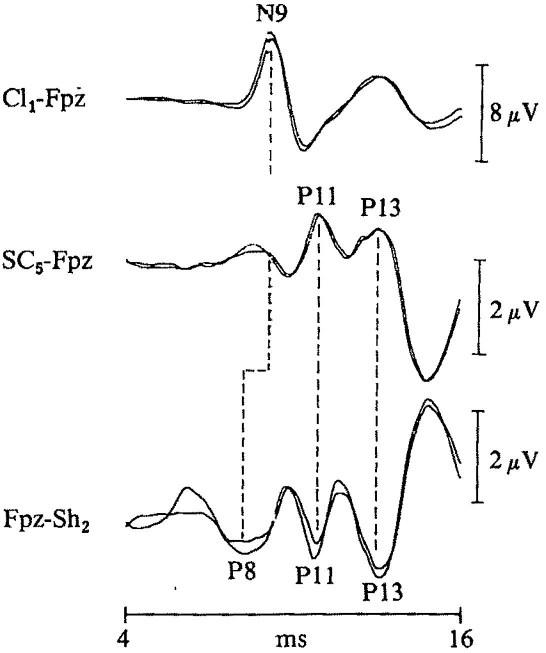

FIG. 9 Somatosensory evoked potentials to left median nerve stimulation. Comparison of scalp-noncephalic (far field) potentials and potentials evoked at neck-scalp derivation. Filters: 150 to 1500 Hz

Comparison of Neck-scalp and Cephalic Far Field Potentials

Fig. 9 compares the far field potentials of Fpz recorded with a noncephalic 'reference' and the potentials obtained at a neck-scalp derivation. The far field potentials of Fpz are almost identical to the potentials recorded at SC_5-Fpz but of opposite direction. This suggests strongly that the potentials P11 and P13 recorded from the neck-scalp derivation are picked up almost exclusively from grid II, namely, Fpz. P11 and P13 have *identical latencies* and similar but not identical amplitudes in lines 2 and 3, whereas P8 is of significantly lower amplitude and longer duration (line 3) than at the scalp-shoulder derivation (line 1). P8 occurs slightly before N9.

Potentials Recorded at the Neck

Fig. 10 shows that at the lower neck (SC_5) two negative potentials occur, labelled, respectively, N10 and N12. N10 occurred 0.96 ms before P11 and N12 1.07 ms before P13. In one case N10 was completely absent and N12 almost absent at the SC_5-SH_2 derivation but P11 and P13 were present in the SC_5-Fpz derivation (fig. 11). We can conclude, therefore, that the neck-scalp derivation is a mixture of four different potentials: two positive peaks picked up by Fpz (P11 and P13) and two negative potentials picked up by SC_5 (N10 and N12). In normal controls, however, only the two positive peaks, P11 and P13, appear as identifiable upward deflections at the neck-scalp derivation (figs. 1, 2, 6, 7, 9, 10).

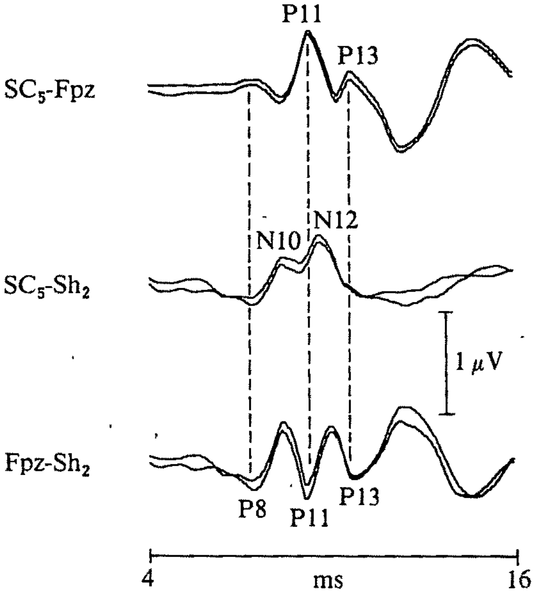

FIG. 10 Comparison of neck-scalp, neck-noncephalic reference and scalp-noncephalic (far field) potentials evoked by left median nerve stimulation.

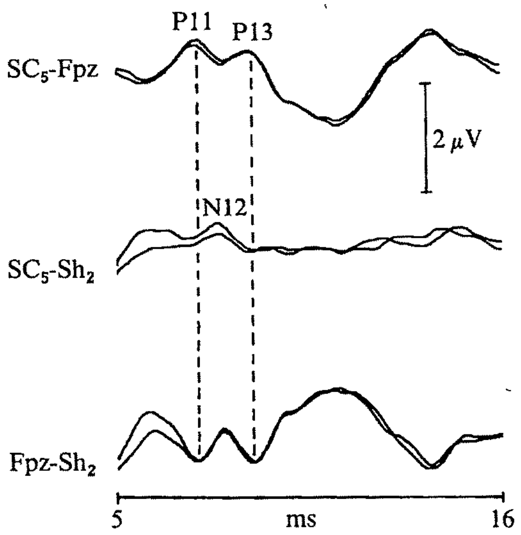

FIG. 11. Comparison of neck-scalp, neck-noncephalic reference and scalp-noncephalic (far field) potentials evoked by left median nerve stimulation.

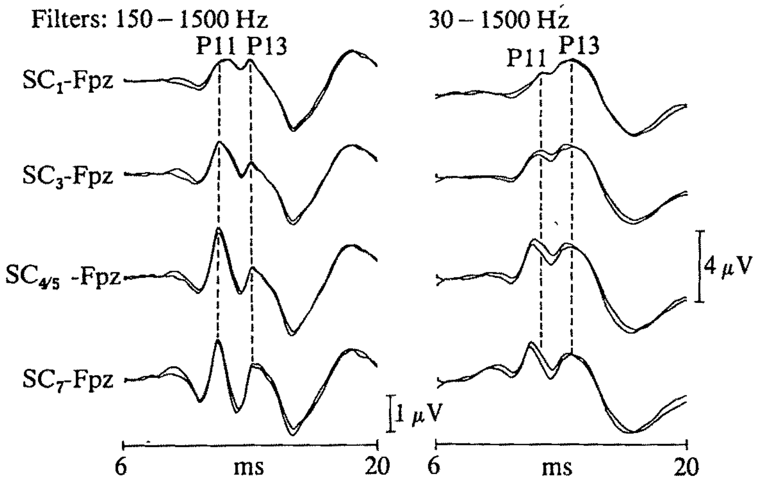

FIG. 12. Effect of filter setting on potentials evoked by left median stimulation and recorded from neck-scalp derivation.

Neck-scalp Derivation: Recording at Different Cervical Levels

Fig. 12 illustrates recordings from different cervical levels against Fpz in grid II. P11 and P13 are clearly identifiable at all levels but are of progressively lower amplitude at higher cervical levels. There is a slight increase of latency of P11 at the high cervical level which is more obvious in the recordings with relatively open LF filters (30 to 1500 Hz). The latency of P13, however, does not change. The effect of opening up the LF filters (*see above*) is essentially the same at all cervical levels.

The constancy of P13 latency and amplitude is obviously consistent with our previous conclusion that P13 is picked up by Fpz. The increase of P11 latency at the high cervical level, however, appears to be contradictory to the assumption that P11 is picked up by Fpz.

Neck Potentials: Recording at Different Cervical Levels

To answer this contradiction, neck potentials recorded from different levels against an 'indifferent' reference (contralateral shoulder) were obtained (fig. 13). In these figures N10 does *not* increase in latency at progressively higher cervical levels but it apparently reverses phase; at SC_7 and SC_6 N10 appears as an upward deflection, at SC_4 there is an apparent isopotential line and at SC_1 a downward deflection of slightly longer latency (labelled P11). N12 shows an *apparent shortening* of latency at higher cervical levels but no phase reversal.

Opening of the LF filters produced a dramatic and fairly selective effect on N12. With LF filters of 150 Hz peak N12 is negligible, but with opening of the LF filter to 30 Hz N12 becomes of much higher amplitude than N10 at all cervical levels. N10 shows the same sensitivity to LF settings found for P11 in fig. 11.

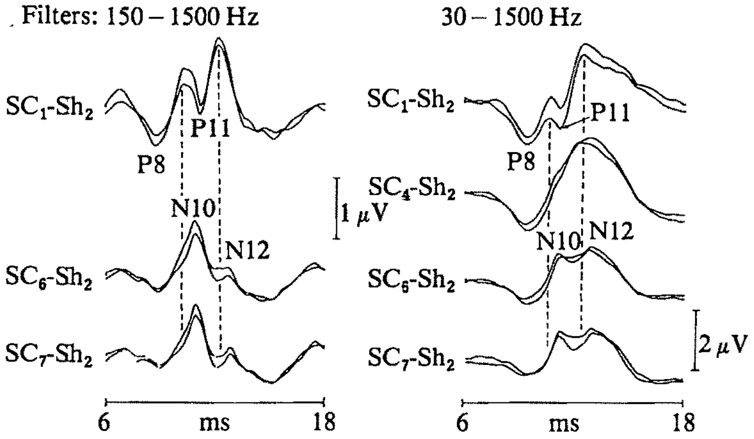

FIG. 13 Effect of filter setting on potentials evoked by left median nerve stimulation and recorded from neck-noncephalic reference derivation.

Comparison of High Cervical Potentials and Far Field Potentials at Fpz

Fig. 14 shows that the early potentials recorded from SC_1 are very similar to the far field potentials recorded from Fpz. Peak P13, however, is not apparent at SC_1 and thereafter the two traces are clearly different. A careful analysis shows also that N10 at SC_7 precedes the 'corresponding' downward deflection at SC_1. This downward deflection at SC_1, however, has a latency identical to the far field P11 recorded from Fpz. We can conclude, therefore, that the downward deflection at SC_1 is actually a far field potential identical to the P11 recorded from Fpz. The first downward deflection, labelled as P8 at Fpz-Sh_2, has an *identical* latency in all three recordings. This potential is also most probably a far field recording of the afferent volley as it passes through the axilla. N12 slightly precedes the far field P13. The upward deflection following P11 at SC_1, however, most probably does not correspond to an 'early' N12 but is a negative far field component similar to the upward deflection recorded between P11 and P13 at Fpz-Sh_2.

Noncephalic References

In the previous discussion we assumed that the contralateral shoulder was an indifferent reference for the recording of far field potentials at Fpz. Fig. 15 shows the recording of far field potentials from Fpz using different noncephalic 'references'. The potentials are similar but not identical in all derivations. To investigate this further we recorded the difference between right shoulder and right hand or foot (fig. 16). This demonstrated that the right shoulder (and to a lesser extent also the right hand) records a relatively prominent triphasic wave with the major negativity having a latency similar to N10 at the SH_2-foot derivation. The initial positivity has the same latency as P8 recorded from Fpz-Sh_2.

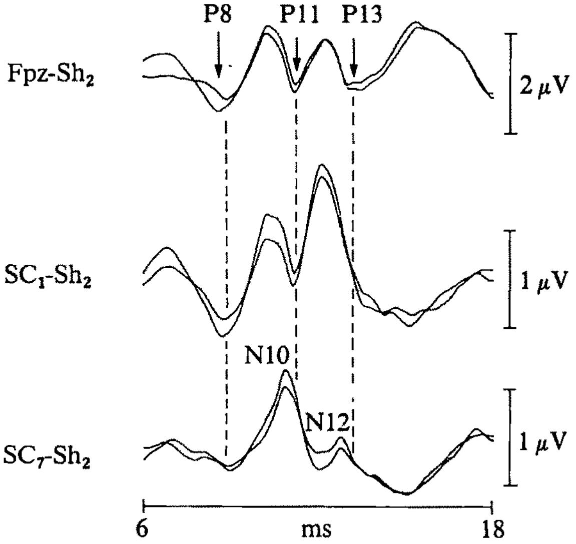

FIG. 14. Comparison of scalp-noncephalic (far field) and neck-noncephalic reference potentials evoked by left median nerve stimulation Filters: 150 to 1500 Hz.

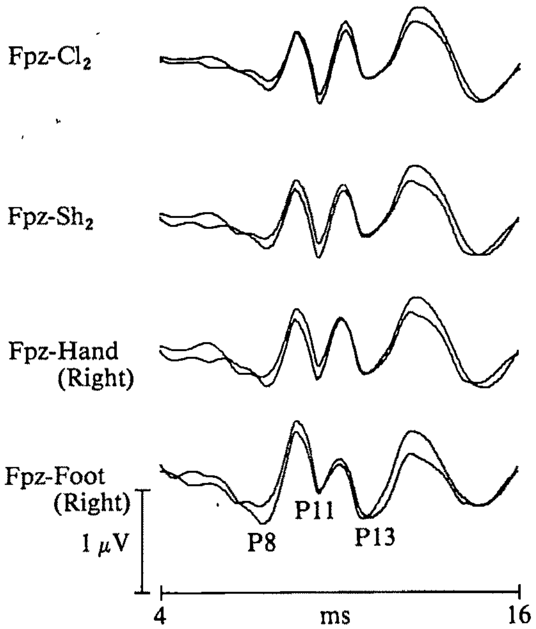

FIG. 15. Recording of far field evoked potentials to left median nerve stimulation using different noncephalic references (contralateral clavicle, contralateral shoulder, contralateral hand and contralateral foot). Filters· 150 to 1500 Hz.

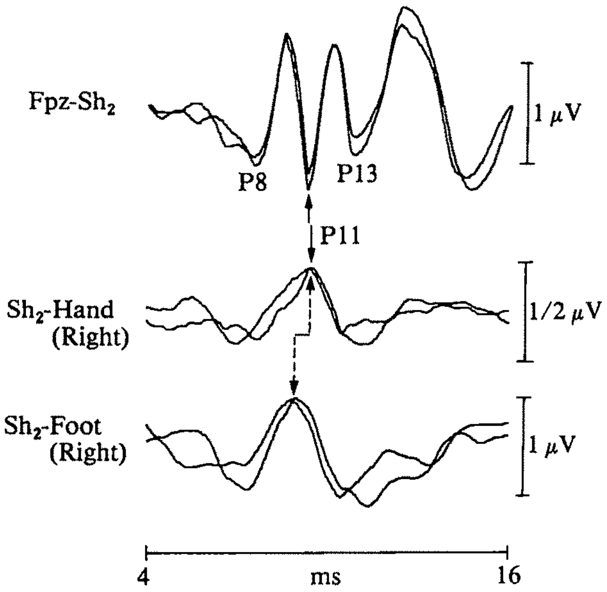

FIG. 16. Far field potentials to left median nerve stimulation recorded from scalp-shoulder, shoulder-hand and from shoulder-foot derivations. Filters 150 to 1500 Hz

Intrasurgical Recordings From Cervical Spinal Cord and Brainstem

Intrasurgical recordings from 2 patients will be presented. The first case is a 19-year-old man with a chondrosarcoma at C6. The abnormality was detected because the patient suffered a mild head injury and cervical x-rays obtained for screening purposes showed an enlargement of the right intervertebral foramen at C5/C6. The patient had no neurological symptoms and presurgical SEPs were within normal limits. Fig. 17 illustrates the recordings from four epidural electrodes and simultaneously obtained far field potentials from Fpz-Sh_2. All four epidural recordings showed typical triphasic waves with a major negative peak whose latency increased slightly in more rostral locations. Peak P11 of the far field potential had a latency of 11.42 ms which corresponded exactly to the peak negativity of the epidural recording obtained from the dorsal rootlets of C6 before they enter the spinal cord. Fig. 18 compares the presurgical neck-scalp recordings with the above-mentioned potentials. The peak P11 had the same latency (11.40 ms) in the presurgical neck-scalp recordings and the intrasurgical far field recordings from Fpz.

Fig. 19 is equivalent to fig. 17 but with LF filters relatively open (30 Hz). The negative peak of the triphasic afferent volley described above shows a minor latency shift of 0.16 to 0.17 ms but essentially *no* change of amplitude. The triphasic wave is now followed, however, by another negative component which is almost completely absent in the recordings with low frequencies below 150 Hz filtered out (*see* fig. 17). This component occurred 1.35 to 2.18 ms after the major negative peak of the afferent wave. The slow negativity was of relatively low amplitude in the lateral recordings from the dorsal rootlet but prominent in the more medial recordings from the dorsal columns.

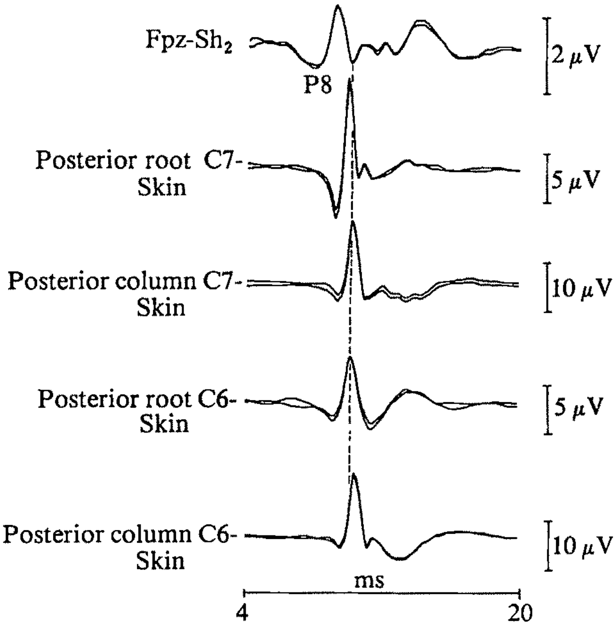

FIG. 17 Simultaneous intrasurgical recording of far field potentials (Fpz-Sh_2) and potentials recorded directly from posterior roots and posterior columns of C6 and C7. Filters: 150 to 1500 Hz.

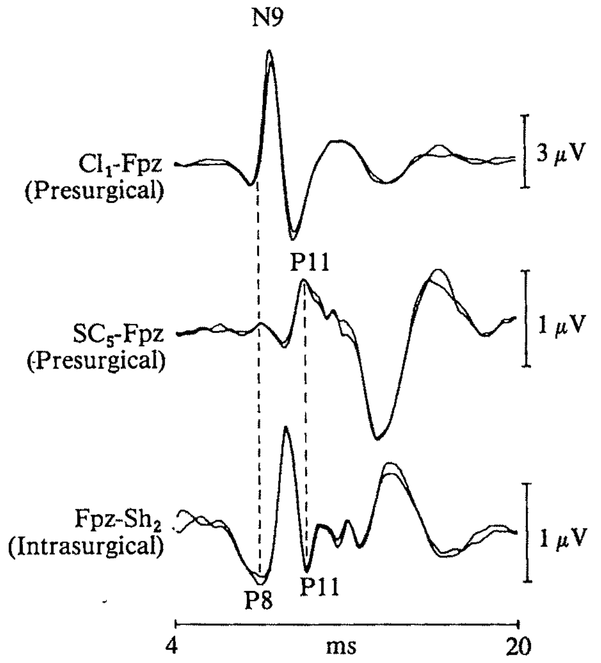

FIG. 18. Comparison of presurgical shoulder and neck potentials (Cl$_1$-Fpz and SC$_5$-Fpz) and intrasurgical far field potentials (Fpz-Sh$_2$) to left median nerve stimulation. Filters: 150 to 1500 Hz.

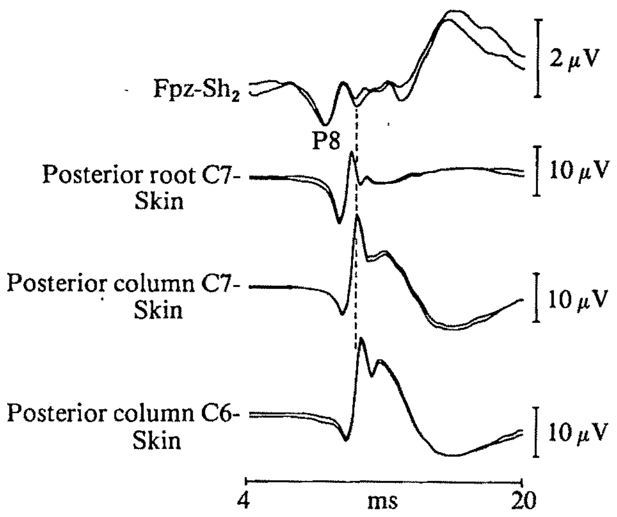

FIG. 19 Simultaneous intrasurgical recording of far field potentials (Fpz-Sh$_2$) and potentials recorded directly from posterior roots and posterior columns of C6 and C7. Filters. 30 to 1500 Hz.

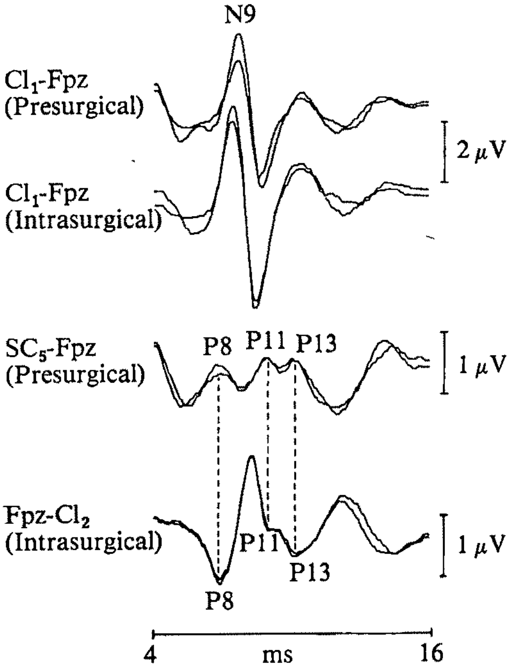

FIG. 20. Comparison of presurgical (Cl$_1$-Fpz and SC$_5$-Fpz) and intrasurgical recordings (Cl$_1$-Fpz and Fpz-Cl$_2$). Filters: 150 to 1500 Hz.

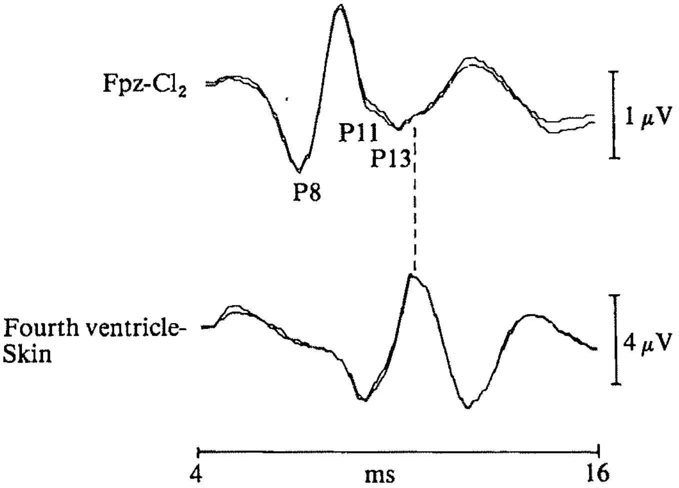

FIG. 21. Intrasurgical recording of far field potentials (Fpz-Cl$_2$) and potentials recorded directly from the fourth ventricle. Filters: 150 to 1500 Hz.

The second case was a patient with syringobulbia and obstructive apnoea secondary to vocal cord paresis. The routine subcortical and cortical SEPs to left and right median nerve stimulation were within normal limits.

Fig. 20 shows presurgical and intrasurgical surface evoked potentials. Channel 1 and 2 illustrate that the potentials recorded from the clavicle ipsilateral to the stimulus (N9) are almost identical, indicating that under both conditions the incoming afferent volleys were comparable. Channels 3 and 4 show that the presurgical P11 and P13 from SC_5-Fpz had the same latency as the corresponding intrasurgical far field potentials. Fig. 21 shows that the negative peak of the afferent volley recorded directly from the fourth ventricle had a latency 0.59 ms longer than the far field potential P13.

DISCUSSION

The results indicate that in the commonly used neck-scalp derivation a complex mixture of potentials is recorded: two negative potentials (N10 and N12) which are picked up from the neck electrode and two positive potentials (P11 and P13) which are recorded from the scalp. All these four potentials tend to produce upward deflections in a neck-scalp derivation. Usually, however, only the two positive potentials (P11 and P13) from the scalp electrode (Fpz) produce identifiable upward peaks in the neck-scalp derivation. The main reason for this is that the far field potentials P11 and P13 tend to be of higher amplitude than the neck negativities N10 and N12. It must be recognized, however, that the two neck negativities also contribute significantly to the generation of these two upward deflections in neck-scalp derivations.

Intrasurgical studies provided direct evidence that P11 is generated in the dorsal rootlets of C6 and that P13 is generated in the dorsal columns at the level of the foramen magnum. By latency considerations we can conclude, therefore, that N10 is generated slightly distal to the dorsal rootlets of C6 and that N12 is generated slightly rostral to the dorsal rootlet of C6. This implies that N10 is actually an expression of the afferent volley *before* it enters the intervertebral foramen and that N12 occurs in the spinal cord approximately at the level where the afferent roots from the median nerve make synaptic connections in the dorsal horn.

We know from comparing EEG tracings in patients with and without skull defects that the skull produces a highly significant attenuation of recorded brain activity. It seems logical, therefore, to assume that electrodes at the neck will preferentially pick up the afferent volley *before* it enters the intervertebral canal, whereas the afferent volley within the spinal cord would be obscured by other potentials of relatively higher voltage. The fact that N10 did not show an increase of latency when recording from progressively more rostral cervical levels is in support of this theory. At high cervical levels, N10 was progressively replaced by the far field P11. P11 is actually generated by the afferent volley at the low cervical level and, therefore, we would expect to pick up its far field component at the high cervical level. N10 consists of frequency components mainly over 250 Hz. This is consistent with the frequency composition of the afferent volley recorded intrasurgically directly from the dorsal rootlets.

From latency considerations, component N12 occurred between P11 and P13. N12 consisted mainly of low frequency components of less than 250 Hz and was extremely sensitive to filtering out low frequencies. N12 had a widespread distribution over the cervical area with essentially no change in latency or amplitude between C7 and C3. At the high cervical level (C1) some of the far field potentials following P11 are recorded and this falsely suggests a paradoxical decrease in latency and increase in amplitude of N12. Intrasurgical recordings directly from the spinal cord demonstrated that the afferent volley was followed by a second component which was extremely sensitive to filtering out slow frequencies. This component was not picked up when recording in the vicinity of the dorsal rootlet but it was prominent more medially when recording from the dorsal columns. All this evidence supports the conclusion that N12 represents the postsynaptic negative cord dorsum potential which is generated by the neurons of the dorsal grey matter ipsilateral to the stimulus and mainly in the spinal cord segments innervated by the median nerve (C6 and C7) (Gasser and Graham, 1933; Bernhard, 1953; Lindblom and Ottoson, 1953*a*, *b*). N12 occurred approximately 2 ms after N10 which is similar to the delay reported between the initial spike potential and the negative cord dorsum potential. This is 1.3 ms according to Bernhard (1953) and 1.9 ms according to Hattori *et al.* (1979). This difference is similar to the intrasurgically recorded latency difference of the peak of the negative afferent potential and the peak of the following slow negativity (1.3 to 2.18 ms). The duration of these potentials is also similar: 3.5 to 5.0 ms for N12 when the low frequencies were open, 5 to 6 ms for the slow negativity recorded intrasurgically and 5 to 15 ms for the negative cord dorsum potential (Gasser and Graham, 1933; Bernhard, 1953; Lindblom and Ottoson, 1953*a*). Latency considerations actually cannot be used to localize precisely this standing potential which most probably is a postsynaptic event in the dorsal horns of C6 and C7 and which, due to its relatively long duration, occurs simultaneously with the afferent volley travelling up the dorsal columns in the high cervical cord. It is well known in electroencephalography that fast frequencies are significantly more attenuated than slow frequencies by the skull. It is likely, therefore, that the neck electrode picks up the slow postsynaptic dorsal horn potentials whereas the potentials of the afferent volley in the dorsal columns are almost completely obscured by the bony structures of the spinal canal.

Neck-scalp Derivation

We mentioned above that in the neck-scalp derivation (SC_5-Fpz) a mixture of 4 major potentials which have *different latencies and are generated in different structures* are recorded: N10 and N12 picked up as near field negativities from the neck electrode and P11 and P13 picked up as far field potentials from the scalp electrode. These potentials are preceded by a low amplitude deflection (P8) which is actually recorded as a positivity from both electrodes, SC_5 and Fpz. P8 is recorded as an upward deflection at SC_5-Fpz because Fpz is relatively more positive (Cracco and Cracco, 1976; Desmedt and Cheron, 1980; Yamada *et al.*, 1980; Anziska and Cracco, 1982). P8 most probably reflects the far field potentials of the afferent volley at the level of the axilla (Cracco and Cracco, 1976; Jones, 1977; Chiappa *et al.*, 1980; Desmedt and Brunko, 1980; Yamada *et al.*, 1980; Anziska and Cracco, 1982). It is difficult to understand, however, why P8 is of higher amplitude at the electrode more distant from the generator, namely, at Fpz rather than at SC_5. A possible explanation is to assume a diagonally orientated dipole with the major positivity orientated towards the head and high cervical region and the following negative pole affecting partially the lower cervical region and thereby tending to cancel out the positivity at that level.

The fact that in the neck-scalp derivation the neck electrodes record negative potentials and the scalp electrode positive potentials has been recognized before (Cracco and Cracco, 1976; Jones, 1977; Desmedt and Cheron, 1980; Yamada *et al.*, 1980; Anziska and Cracco, 1981). Other authors, however, neglected the possibility of an active 'reference' in the discussion of potentials recorded from the neck-scalp derivation (Matthews *et al.*, 1974; El-Negamy and Sedgwick, 1978; Hume and Cant, 1978).

Jones (1977) and Yamada *et al.* (1980) observed identical latencies for the negative neck potentials and positive far field potentials. They assumed that the positive potentials at the scalp were the far field reflection of *the same generators* which produced the corresponding negativities in the neck. Cracco and Cracco (1976) and Anziska and Cracco (1981) recorded a broad negativity from neck electrodes but were unable to distinguish two components, indicating only that the peak of the neck negativity had a latency approximately equal to P13. Desmedt and Cheron (1980) distinguished two neck negativities, the first one occurring at the same time as the far field P11 and forming a shoulder on the major negativity from the neck. They did not comment on the latency of the major negativity but in their figures it is obviously not identical to the later (P13, P14) far field potentials from the scalp. These authors assume *different generators* for the neck negativities and the scalp positivities but their use (Cracco and Cracco, 1976; Desmedt and Cheron, 1980; Anziska and Cracco, 1981) of open LF settings with the corresponding selective enhancements of the second major neck negativity (N12 in our terminology) makes it difficult to recognize the early negative neck potentials. In our recordings using 150 to 1500 Hz filters the first negativity N10 can be always clearly distinguished and in the majority of the cases is actually the most prominent component.

As indicated in the Introduction, in the clinical application of somatosensory evoked potentials, the neck-scalp derivation is probably more popular than the scalp-noncephalic reference montage. The main reason for this is that the scalp-noncephalic reference montage is usually significantly more noisy than the neck-scalp montage (the shoulder usually contains twice the noise recorded from SC_5, and the contralateral hand or foot tends to be even noisier) (Desmedt and Cheron, 1980; Anziska and Cracco, 1981). This is probably one of the explanations why Chiappa *et al.* (1980) could not identify the three main far field potentials from the scalp in 10 to 22 per cent of the cases, whereas they observed a clearly defined P13 in all cases and P11 in 94 per cent of the cases in neck-scalp derivations. The other explanation is that in the neck-scalp derivation the neck negativities in grid I add with the scalp positivities in grid II tending to produce relatively higher amplitude potentials (Chiappa *et al.*, 1980). Because of the technical difficulty in obtaining good far field recordings using scalp-noncephalic derivations, Chiappa *et al.* (1980) have recently abandoned its routine use.

We feel that neck-scalp derivations are the most useful in clinical studies of somatosensory evoked potentials to median nerve stimulation. For proper evaluation of the results, however, a good understanding of all the generators contributing to the potentials is essential. We feel, therefore, that the use of a noncephalic 'reference' such as the contralateral shoulder is an extremely informative complement to the neck-scalp derivation. For example, Maugière and Courjon (1981) reported on a case with an astrocytoma in the dorsal medulla and right dorsal column funiculus in which an upward deflection could be recorded at SC_7-Fz and SC_2-F7 but no far field P13 at a parietal-ears derivation. The upward deflection at the neck-scalp derivations was of low amplitude and most probably was a reflection of N12, whereas the absence of P13 can be explained by the lesion of the dorsal columns at a higher level.

Desmedt and Cheron (1980) recommended that in neck-scalp recordings an upper cervical electrode should be used because at that derivation P8 cancels out and, therefore, the onset of the spinal activity is more easily estimated. The downward deflection at neck-scalp derivations which follows the initial P8 is mainly an expression of the scalp far field negative component between P8 and P11. This component has a latency similar, but not necessarily equal, to N10 and is usually of significantly higher amplitude. This determines that a well-defined downward deflection (negativity at Fpz) separates P8 from P11 at a low neck-scalp derivation. High neck derivations start to pick up not only the scalp far field P8 but also the scalp far field P11. The scalp negative far field potential between P8 and P11 tends, therefore, to cancel out even more at high neck-scalp derivations. Summarizing, we feel that the downward deflection between the peaks P8 and P11 of the neck-scalp derivation is mainly an expression of far field potentials (not a near field recording of the onset of spinal activity as suggested by Desmedt and Cheron (1980)). It is less well defined in high cervical than in low cervical-neck derivations due to cancellation effects. As mentioned above, near field cervical potentials are consistently obscured by the far field scalp potentials when recording from neck-scalp derivations due to bony attenuation (Anziska and Cracco, 1981).

Chiappa *et al.* (1980) also prefer the use of SC_2-Fz for recordings from neck-scalp derivation. They notice, however, that in this derivation P11 appears only as a shoulder on the upward slope towards P13 and is unidentifiable in 6 per cent of recordings from normal controls. There are two reasons for the poor definition of P11 in their recordings. The scalp far field potential P11 is picked up to a significant degree at the high cervical level and, therefore, partially cancels out at high neck-scalp derivations. In addition, the use of an almost completely open LF setting (3 to 3000 Hz) selectively enhances the neck N12 component and tends to obscure the faster potentials such as P11. Anziska and Cracco (1981) also report absence of P11 in a significant proportion of their control cases (3 out of 9). This was again most probably related to the use of open LF filters (10 to 2500 Hz).

Summarizing, we feel that for recording of P11 and P13 from neck-scalp derivations a low cervical derivation (SC_5 or SC_7-scalp) and the use of a LF setting of 150 Hz has definite advantages. This will avoid cancellation of P11 and better define the fast components which are a reflection of the afferent volley. For precise definition of the peaks which are being recorded in this montage, additional derivations (scalp and neck to a noncephalic 'reference') and opening of low frequencies to 30 Hz may be helpful.

Neural Generators of Far Field Somatosensory Evoked Potentials

The far field potentials recorded from Fpz consists of three major positive deflections which we identified as P8, P11 and P13. There is general consensus that the peak of P8 coincides with the arrival of the afferent volley at the axilla (Cracco and Cracco, 1976; Jones, 1977; Chiappa *et al.*, 1980; Desmedt and Brunko, 1980; Yamada *et al.*, 1980; Anziska and Cracco, 1981). We reported before that in intrasurgical recordings, the P11 and P13 peak (neck-scalp derivation) coincided in time respectively with the peak of the negative afferent volley at the dorsal root entry zone at the level of C6 and at the dorsal columns at or below the foramen magnum (Lesser *et al.*, 1981). Intrasurgical recordings from the spinal cord, however, were compared with surface recordings from neck-scalp montages that were not simultaneous with the intrasurgical tracings. Furthermore, the patients had significant CNS pathology. As mentioned above in patients with CNS pathology, the two major peaks of the response recorded from neck-scalp derivation are not always P11 and P13.

In the first case reported here, far field potentials obtained from Fpz were compared with *simultaneously* recorded intrasurgical potentials in a patient with no neurological signs or symptoms and with normal presurgical somatosensory evoked potentials. The results confirm our previous conclusion that P11 is generated at the dorsal rootlets at the level of C6. In the second case we demonstrated that the simultaneously recorded far field component P13 occurred before the afferent volley reached the caudal portion of the fourth ventricle, again supporting our previous conclusion that P13 is a reflection of the afferent volley as it reaches the foramen magnum. This patient had motor signs but no sensory deficit and normal presurgical somatosensory evoked potentials.

Our conclusion that P11 represents the afferent volley in the dorsal rootlets of C6 is in good agreement with current theories of other authors. By simple latency considerations, Jones (1977) concluded that P11 (N11 in his terminology) must be generated immediately adjacent to or just within the spinal cord, and recently Desmedt and Brunko (1980) and Desmedt and Cheron (1980) calculated that the arrival of the sensory volley at the spinal cord coincided with the onset latency of P11. Yamada *et al.* (1980) reached similar conclusions. Cracco and Cracco (1976) initially assumed that P11 was a reflection of synaptic and postsynaptic activity in the nucleus cuneatus and median lemniscus. In recent reports they assume a more caudal origin in the spinal cord dorsal columns (Anziska and Cracco, 1980). Chiappa *et al.* (1980) initially concluded from evaluation of somatosensory evoked potentials in patients with intramedullary cord lesions that P11 (A wave in their terminology) originated rostral to the high cervical cord. Recently, however, they also displaced the origin of the early somatosensory evoked potentials caudally when they concluded that P13 (B wave in their terminology) was generated at the level of the foramen magnum (Goldie *et al.*, 1981). Wiederholt (1980) is the only author who localizes P11 (P12 in his terminology) to a level above the foramen magnum, namely, between the posterior columns and thalamus.

There is significantly more discrepancy regarding the origin of P13. Our conclusion that P13 is generated at the level of the foramen magnum is in good agreement with the observation of Goldie *et al.* (1981) that P13 (B wave in their terminology) has been recorded unchanged from patients with brain death and necrosis of the pons and upper medulla suggesting that the generator sources are more caudal and located at the level of the dorsal column nuclei. Similar conclusions were also reached by Jones (1977) ('spinal grey matter or brain stem'), Hume and Cant (1978) ('dorsal column nuclei') and Yamada *et al.* (1980) ('cervical cord'). Cracco and Cracco (1976) initially related P13 to activity in the thalamus and thalamocortical radiations but recently displaced its origin caudally to the brainstem-lemniscal pathway (Anziska and Cracco, 1980). Kritchevsky and Wiederholt (1978) and Wiederholt (1980) speculated that P13 was of thalamic origin and recently Desmedt and Cheron (1980) concluded that P13 was originated above the foramen magnum, in the medial lemniscus.

In all the studies quoted above the basic methodology for defining the generators included latency considerations, distribution of surface potentials and/or observation of somatosensory evoked potentials in patients with neurological diseases. Latency considerations are only accurate if the reference points at which the afferent volley is measured directly are relatively close together. Therefore, Jones's (1977) and Desmedt and Cheron's (1980) conclusion that P11 is generated at the spinal cord entry has an excellent chance of being correct. On the other hand, Desmedt and Cheron's (1980) conclusion that P13 is generated above the foramen magnum is based on indirect calculations of latency using relatively distant reference points (Erb's potential and the initial, probably postsynaptic, cortical potential). This probably explains why there is considerably more discrepancy regarding the origin of P13. Surface distribution studies are an essential tool for the localization of generator sources. However, our theoretical knowledge regarding distribution of far field potentials in a nonhomogenous medium is extremely limited. For example, in many studies the possibility that a distant reference such as Fpz for neck potentials could be at least as active as the neck electrodes was totally neglected. This necessarily limits greatly the conclusion reached by analysis of the surface distribution of potentials. Clinical correlation studies also have limitations. The precise extent of the lesion can only be determined by pathological studies which are performed at variable times after the recordings were obtained. Besides, pathological lesions frequently disrupt function of nervous tissue located at a considerable distance from the primary lesion; this is extremely difficult to evaluate even when pathological studies are available. We feel that the most reliable method for localization of a spinal cord generator source is the *simultaneous* recording of surface potentials and direct recordings from the major afferent somatosensory pathways. Recordings from the dura overlying the dorsal columns permit precise evaluation of the main spinal cord afferent volley. This allows exact determination of where the afferent volley was at the time any given peak of a far field evoked potential occurred. We agree with the criticism of Arezzo *et al.* (1979) that it is 'not possible to identify the intracranial source of a surface recorded potential by demonstrating a concurrent waveform with a single brain site because continuing activity within the more caudal portions of the somatosensory pathways may produce potentials that sum with those generated more rostrally'. This criticism does not apply, however, to the potentials recorded from the peripheral nervous system or spinal cord. In the peripheral nervous system there is no significant activity after the afferent volley passed through, and in the spinal cord the only continuing activity would be the dorsal cord potential. By direct surface recording from the neck with noncephalic references and by filtering out the slow components we have been able to isolate the dorsal cord potential and exclude the possibility that it participates in the generation of P11 or P13.

There is no good explanation for the mechanisms of generation of the different far field potentials recorded from the scalp. The afferent volley should obviously produce a broad positivity as it approaches the recording electrode. Nevertheless, why are there three distinct positive peaks? These peaks tend to be of relatively short duration (1 to 2 ms) and, when filtering out the slow frequencies under 150 Hz, the far field potentials consist of positive and negative deflections of approximately equal amplitude (deflections above and below the baseline are approximately equal). Opening up the LF setting produces a long duration positivity with all peaks below the baseline. The short duration of the peaks and relative insensitivity to filtering out low frequencies is consistent with the assumption that the far field potentials are mainly a reflection of the afferent volley. This is in good agreement with Lorente de Nó's (1947) observation that subcortical nuclei produce mainly closed fields which will not be recorded at a distance and with the conclusion of Arezzo *et al.* (1979) from experimental studies in monkeys that the nucleus cuneatus and ventrobasal thalamus produce no far field potentials. It is interesting to notice that the three far field peaks (P8, P11 and P13) occurred at points where there is an abrupt expansion of the structures surrounding the afferent pathways: P8 at the axilla when the nerve becomes surrounded by the cervicothoracic muscle groups, P11 at the spinal cord when the afferent volley enters the spinal canal and P13 at the foramen magnum when the afferent volley enters the skull. It is tempting to speculate that the far field peaks are produced by an abrupt change of current flow when there is a major change in the physical characteristics of the medium surrounding the nerve or tract in which the afferent impulse travels. The approaching of the afferent volley to the recording electrode would produce a progressively increasing positivity. When the afferent volley enters into a cavity, however, there would be a sudden increase of resistance between the generator source and the surface recording electrode. This would determine a sudden decrease of current flow and, therefore, less positivity is recorded, generating a peak. Experimental evidence in support of this hypothesis was presented recently by Nakanishi (1982).

Potentials Recorded from Neck Electrodes

In direct recordings from the dura we were able to differentiate two components: an initial triphasic wave of short duration which consisted mainly of frequencies above 250 Hz and a following long duration negative wave consisting of frequencies mainly below 250 Hz. This later component was almost completely absent in recordings from the lateral spinal cord. We interpreted the initial triphasic wave as the afferent volley and the following slow negativity as the dorsal cord potential (Gasser and Graham, 1933; Bernhard, 1953; Lindblom and Ottoson, 1953*a*, *b*). These observations are identical to those of Ertekin (1978). Shimoji *et al.* (1972) described a different waveform consisting of an initial positivity followed by a prominent negativity. They assumed that the positivity reflected the afferent volley and the negativity was the dorsal cord potential. In some cases they observed a bifid negativity. This strikingly different waveform was most likely the consequence of using different filter settings. Shimoji *et al.* (1972) used a setting of 1 to 100 Hz which filters out almost completely the triphasic afferent volley. In later reports (Shimoji *et al.*, 1978) they opened up the high frequency filter settings to 3000 Hz and in all these figures an early, short duration negativity is clearly visible.

Previously (Lesser *et al.*, 1981) and to a lesser degree in this study, we demonstrated that when recording directly from the dura of the spinal cord a travelling triphasic afferent volley can be recorded. By filtering out frequencies below 150 Hz this afferent volley can easily be isolated from the dorsal cord potential. It is interesting to note, however, that from the surface of the neck, both neck negative potentials N10 and N12 were standing potentials: we could not identify a travelling wave. N10 was an expression of the afferent volley *before* it entered the spinal canal and N12 an expression of the dorsal cord potential. The afferent volley in the dorsal column was most probably obscured by the dorsal cord potential because of the selective attenuation of fast frequency components by bony structures.

Previous investigators who used neck-scalp derivations have also suggested that the neck potentials have fixed latencies and, therefore, fixed generators (Matthews *et* *al.*, 1974; El-Negamy and Sedgwick, 1979; Small *et al.*, 1980). In that montage, however, the scalp far field potentials (P11, P13 of grid II) are the main determinants of the two principal upward peaks (Anziska and Cracco, 1981). Changing the neck electrode in grid I will therefore have little effect. The only reliable way to record neck potentials uncontaminated by far field scalp potentials is to use a distant noncephalic reference, but this method also has significant pitfalls. Electrodes placed just rostral to a far field potential generator will record the corresponding far field potentials. Therefore, at the lower neck, P8 is picked up and at the higher neck, ear, and inion, P8, P11 and the subsequent negative far field deflection are picked up. These far field potentials should not be confused with near field neck potentials. For example, Desmedt and Cheron (1980, fig. 1) identified at the upper neck a positivity which they suggested indicates the arrival of the afferent volley at that level. This peak, however, has a latency identical to P11 and most probably is a far field potential reflecting the arrival of the afferent volley at the lower cervical spinal cord. Cracco (1972), Cracco (1973), and Cracco *et al.* (1980) described a triphasic wave at neck-ear derivations which had a tendency to increase in latency from low to high cervical derivations. We noticed a similar apparent increase of latency which we demonstrated by the use of noncephalic references to be due to the appearance of far field potentials at the high neck derivation. Fixed latencies for neck negativities were reported in other studies in which noncephalic references were used and in which the fact that far field potentials are picked up at high cervical levels was considered (Jones, 1977; Jones and Small, 1978; Yamada *et al.*, 1980). The only exception is Yamada *et al.* (1980) who in some but not all cases described a travelling wave N12 (N13 in their terminology).

In their early studies, Jones (1977) and Jones and Small (1978) assumed that the neck negativities and far field scalp potentials were generated by the same sources (bipoles). Yamada *et al.* (1980) also made similar assumptions. They most probably reached their conclusions because they neglected small but consistent latency differences between the neck negativities and the scalp positivities. Recently, however, Jones *et al.* (1980) considered the possibility that the main neck negativity N12 (N13 in their terminology) could be due to different generator sources than P13.

There is general consensus that the early negativity recorded from the neck (N10) reflects an afferent volley. The only exception is the report by El-Negamy and Sedgwick (1978) who, from recovery function studies, concluded that N10 was postsynaptic in nature. They used open low frequency filter settings in which N10 appears as a shoulder on N12. Under these recording conditions it is very likely that the recovery function of N12, which starts before the peak N10, contaminated the results. The observation of Yamada *et al.* (1980) that N10 (N11 in their terminology) is consistently lateralized and of slightly shorter latency at electrodes 5 cm lateral to the spinal cervical processes is of interest. It clearly supports our conclusion that N10 is generated at the entry of the afferent volley into the spinal canal. Regarding the second neck negativity (N12) it is important to point out that most authors used open low frequency filter settings which, as indicated above, make differentiation of two distinctive neck negativities (N10 and N12) more difficult. Desmedt and Cheron (1980) indicate that it is 'difficult to differentiate in the neck somatosensory evoked potential profile the respective contributions of the interneuron potentials of the dorsal horn and of the volley ascending in the dorsal columns' and they assume that the abrupt front of N12 reflects the ascending volley. Anziska and Cracco (1981) reached similar conclusions. They were unable clearly to identify two components but speculated that the initial portion of the main neck negativity (N12) reflects presynaptic activity whereas the subsequent portion is postsynaptic. Pratt *et al.* (1980) also concluded from studies of the recovery function that the main neck negativity was of postsynaptic nature. Only Kimura *et al.* (1978) and Yamada *et al.* (1980) described N12 (N13 in their terminology) as a travelling wave (in some but not all cases) and assumed, therefore, that it reflected the ascending volley in the cervical dorsal columns.

Noncephalic References

The contralateral shoulder or hand has been used by many authors as noncephalic indifferent reference (Cracco and Cracco, 1976; Green and McLeod, 1979; Arezzo *et al.*, 1979; Desmedt and Cheron, 1980; Anziska and Cracco, 1981). However, Cracco and Cracco (1976) demonstrated that the hand contralateral to the stimulus actually recorded a positivity (P8) when referred to the knee and we demonstrated above that the shoulder contralateral to the stimulus and also to a lesser extent the corresponding hand not only records a broad positivity but actually a broad triphasic wave with the initial positivity having a latency similar to P8 and the following major negativity a latency corresponding approximately to N10. We can conclude, therefore, that the shoulder and hand 'see' the afferent volley as it approaches the spinal cord (initial positivity, P8), as it passes through the base of the neck up to the point where it enters the spinal cord canal (major negativity, N10) and as it moves away from the electrodes ascending through the dorsal columns (following positivity). The negativity at the shoulder thus cancelled out part of the neck negativities (particularly N10) and falsely enhanced the far field positivity P11 in the Fpz-Sh_2 montage.

Filter Settings

Many authors report difficulties in differentiating a clearly defined P11 (Hume and Cant, 1978; Chiappa *et al.*, 1980; Strenge *et al.*, 1980; Yamada *et al.*, 1980). This is probably related to the use of open LF filters.

Desmedt *et al.* (1974) stressed the need for open HF settings for adequate definition of early cortical somatosensory evoked potentials. The same principle also applies to the recording of subcortical somatosensory evoked potentials, and in most reports of subcortical somatosensory evoked potentials the HF settings were of 1000 Hz or more. There are only very few exceptions (Arezzo *et al.*, 1979; Colon *et al.*, 1977; Fukushima *et al.*, 1976; Spudis *et al.*, 1980).

On the other hand the LF filters were usually set at less than 30 Hz in an attempt to record the 'true' waveform. The only exceptions are Green and McLeod (1979) and Wiederholt (1981) who used filter settings of 100 Hz. We feel that filters should be set to filter out as much as possible of the components not of direct interest, while influencing as little as possible the components it is wished to record, regardless of how narrow the bandpass may be. Frequently the decision as to what filter setting to use is a compromise between these two factors. When recording subcortical somatosensory evoked potentials we are primarily interested in recording the afferent volley. The afferent volley mainly has frequency components between 250 and 1000 Hz. Therefore, we recommend filter settings of 150 to 1500 Hz which will accurately record the afferent volley but filter out other contaminating frequencies (60 Hz artefact, EEG waves, dorsal cord potential, etc.). With these filter settings, the afferent volley is of slightly lower amplitude than if open LF settings are used, but the recording contains significantly less noise. Filtering out of the slow dorsal cord potential permits better differentiation of P11 from P13 and most probably explains why we were able to distinguish a clearly defined P11 in all the controls despite averaging only 400 stimuli. On the other hand, for recording of the dorsal cord potential, LF settings of 30 Hz or less should be used.

Amplitude of Subcortical Somatosensory Evoked Potentials

In a previous report we observed that the logarithm of the amplitude but not the absolute amplitude of somatosensory evoked potentials had a normal distribution (Lueders, 1970). In this study we observed that the same is also true for subcortical somatosensory evoked potentials. This is important for clinical studies because it implies that unless logarithms are employed, the use of mean amplitudes and standard deviations to define limits of normality is not only inaccurate but also produces absurd numbers (that is, negative amplitudes). Another useful parameter for analysis of amplitude is the ratio between left- and right-sided stimulation. Again, since the logarithm of amplitude has a normal distribution we advise the use of the logarithm of the ratio when applying statistical analysis.

Kritchevsky and Wiederholt (1978) recommended the use of bilateral stimulation for better definition of the peaks. Bilateral stimulation is not only useful for definition of peaks but also for obtaining the ratio of bilateral to unilateral stimulation (again we recommend the use of the logarithm of the ratio for statistical analysis). In patients with marked asynchrony between the two sides the response to bilateral stimulation tends to be of abnormally low amplitude. The same is also true for potentials evoked using other stimulus modalities (Lueders, Lesser and Klem, 1981).

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NOT 'INDIFFERENCE TO PAIN' BUT VARIETIES OF HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY

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SUMMARY

Three children, from different kinships, with generalized insensitivity to pain, showed unusual manifestations of congenital, presumably inherited, sensory and autonomic neuropathy. The first child appeared to have a syndrome resembling those previously described as congenital indifference to pain, congenital universal insensitivity to pain or congenital universal analgesia in that she exhibited a selective and universal loss of pain sensation from infancy without other apparent neurological deficit. Unlike most types of hereditary sensory and autonomic neuropathies (types I, II, III), but like type IV, she had normal sensory nerve action potentials. Abnormalities of sudomotor function and of somatosensory evoked potentials were demonstrated. A severe decrease in the number of sural nerve A delta fibres and a small reduction in C fibres were demonstrated morphometrically. An abnormality of C fibres was confirmed by a marked reduction in nerve dopamine-β-hydroxylase activity. The plasma and CSF concentrations of β endorphins, substance P and several other neuropeptides and hormones were normal. Unequivocal evidence of a neuropathic lesion is provided by this patient; her disorder may be identified as the fifth type of hereditary sensory and autonomic neuropathy. The second patient had a congenital pansensory neuropathy and progressive retinitis pigmentosa. Whether the disorder is inherited and, if so, whether the retinitis pigmentosa results from the same or from a second genetic abnormality, is unclear. The third case has, in addition to what is usually seen in hereditary sensory and autonomic neuropathy, type II, an unusually severe kinaesthetic difficulty in oral food handling. The sural nerves of the second and third patients had fibre composition characteristic of hereditary sensory and autonomic neuropathy, type II, few or no myelinated fibres and reduced numbers of unmyelinated fibres.

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INTRODUCTION

Insensitivity to noxious stimuli (analgesia) is a prominent feature of hereditary sensory neuropathy (here called hereditary sensory and autonomic neuropathy (HSAN)) and is an important factor in the development of various tissue complications (Dyck *et al.*, 1983). Using the mode of inheritance, natural history (onset, course, symptoms and outlook) and population of neurons (or axons) affected, we have tentatively classified HSAN into four types (Dyck and Ohta, 1975). Type I is dominantly inherited; symptoms usually begin in the second, third or fourth decade; sensory and autonomic symptoms tend to affect the feet and legs in particular and a variable degree of peroneal muscular atrophy is usually present. Perforating ulcers and tissue mutilation appear to be related to use, abuse, neglect and possibly other factors (Dyck *et al.*, 1983). Types II, III and IV HSAN are all congenital and may be recessively inherited. Type II patients have a pansensory neuropathy affecting the limbs more than the trunk or face and cutaneous more than deep sensation. Cutaneous nerves are abnormally small and contain reduced numbers of mostly unmyelinated fibres. Type III is a familial dysautonomia, now known to be associated with a severe pansensory disturbance.

Whereas types I, II and III can readily be shown to have neuropathic abnormalities—sensory loss, decreased or absent tendon reflexes, dysautonomia and unequivocal pathological abnormalities of nerve—the syndromes of congenital indifference to pain (Arbuse *et al.*, 1949; Boyd and Nie, 1949), congenital universal insensitivity to pain (McMurray, 1950; Feindel, 1953; Baxter and Olszewski, 1960) and congenital analgesia (Dearborn, 1932) were not reported to have neuropathic abnormalities. These patients were, however, studied prior to the application of methods to assess the physiological function of afferent nerve fibres *in vivo* and *in vitro* (Buchthal *et al.*, 1975; Lambert and Dyck, 1975) and prior to the use of improved histological, microscopic and morphometric methods (Dyck and Karnes, 1981). It is, therefore, unclear whether a neuropathic abnormality was in fact absent or merely unrecognized. The problem was further complicated when some authors used the term 'indifference to pain' for cases with obvious sensory neuropathy. A clue that some of the cases of congenital universal insensitivity to pain had a neuropathic abnormality came from the study of male siblings reported by Swanson (1965), Swanson *et al.* (1965) and Pinsky and DiGeorge (1966). In these patients, a congenital absence of small fibres in peripheral nerve and spinal cord was demonstrated (Swanson *et al.*, 1965). Later studies by others showed that unmyelinated fibres, in particular, were strikingly decreased in number in the sural nerve (Bischoff and Curti, 1977; Goebel *et al.*, 1980). These patients with type IV HSAN might not, therefore, be expected to show abnormalities of tactile sensation, tendon reflexes or cutaneous nerve action potentials.

This report, describing another case of congenital universal insensitivity to pain, provides a fifth type of HSAN and further evidence of a neuropathic abnormality which would not have been recognized by former methods of assessment. The second and third cases of congenital HSAN reported here had, in addition to severe congenital pansensory neuropathy and morphometric features typical of the type II disorder, retinitis pigmentosa in Case 2 and severe constipation and problems with oral food handling in Case 3.

MATERIALS AND METHODS

Sensory Testing

The young age of Cases 1 and 3 precluded testing of their sensation with computer assisted sensory systems. For them, the parent's history, observation at play and clinical examination had to suffice. For Case 2, computer assisted sensory testing was attempted but, because of his poor vision from retinitis pigmentosa, could not be performed.

Sudomotor Function

When Case 1 was placed in a heat chamber, her core temperature was raised by 0.6° C. Her ability to sweat was assessed by visual inspection.

Compound Action Potential of the Sural Nerve in Vitro

The compound action potential was recorded from fascicles of sural nerve suspended from silver electrodes in a chamber through which moistened 95 per cent oxygen and 5 per cent carbon dioxide were passed. The technique, normal values and correlation with the morphometric measurements in health and disease have previously been published (Lambert and Dyck, 1975).

Axonal Flow of Dopamine-β-hydroxylase (DBH) and Acetylcholine Esterase (AChE)

The techniques for assessing the content and redistribution of the naturally occurring enzymes DBH and AChE, *in vitro* have been reported for sural nerve in health and in various neuropathic disorders (Brimijoin and Dyck, 1979).

Sural Nerve Biopsy and Control Nerves

Whole sural nerve biopsy was performed on these patients at ankle level without the use or need of a local anaesthetic. Control nerves were obtained at post-mortem.

Histological Technique and Morphometric and Teased Fibre Assessment

Nerves were fixed in 2.5 per cent glutaraldehyde in 0.025 M cacodylate buffer at pH 7.38 and 10° C for 45 min for teased fibres and for 24 h for embedding into epoxy resin. After osmication, portions of nerve specimen were glycerinated for preparation of teased fibres or embedded into epoxy resin for morphometric assessment. Semithin transverse sections were stained with phenylene diamine and evaluated by computer imaging (Zimmerman *et al.*, 1980). The morphometric approaches have been described (Dyck, 1975; Dyck and Karnes, 1981). Nonoverlapping electronmicrographs were obtained from thin transverse sections for evaluation of the number and size of unmyelinated fibres.

Analysis of Peptides in Plasma and CSF

The content of endorphins (Kao and Heser, 1980), substance P (Mroz and Leeman, 1979), met-enkephalin (Sarne *et el.*, 1978; Clement-Jones *et al.*, 1980), cholycystikinen (CCK), vasoactive intestinal peptide (VIP) (Chang and Chey, 1980), human pancreatic polypeptide (HPP) (Floyd, 1980) and neurotensin (Carraway, 1979) were determined by radioimmunoassay (RIA). ACTH was determined according to the method of Kao *et al.* (1979).

RESULTS

Case 1

Clinical assessments. Because this 26-month-old girl was adopted, a detailed kinship history could not be obtained and kin could not be examined. The mother was a 14-year-old, primigravida, healthy girl who had an uncomplicated pregnancy and vaginal delivery and who had not ingested alcohol or drugs during the pregnancy. Consanguinity was suspected, but not confirmed. As an infant, the patient fed poorly and was hypotonic. When adopted at 5 months, her adoptive mother noted that she was 'floppy', did not react to pain when blood was drawn and appeared to be irritable during periods of hot weather when her body temperature was found to be elevated (up to 39° C). Her teeth, which erupted at the usual age, were lost prematurely, perhaps as a result of excessive chewing of foreign objects, lips and tongue. With excitement, anger or crying she developed a blotchy red colour on her face. Her mother reported sweating only over her nose. She sat at 10 months, stood with support at 9.5 months, walked with support at 13 months, walked without support at 23 months and said her first words at 13 months. Her mother thought that her psychomotor development was delayed but not retarded.

As she developed, her parents became concerned about the lack of a pain response. She did not object or cry when her 'hands were spanked' but might 'if her bottom was spanked'. At 15 months she burned her left foot sufficiently to require medical attention, but without having cried or reacted as if in pain. Three weeks later her hand was severely burned also without a pain reaction (fig. 1). The mother said that she cried with overflow tears. She frequently bit her tongue and lips, so that she bled, but without apparent pain. On one occasion, a plastic ruler hit her eye and she 'acted as if hurt'. Sometimes when she fell down and 'banged her head' she cried as though 'she was hurting'. On another occasion she pushed a sharpened pencil through her cheek without crying (fig. 2).

At 26 months of age, her weight was 12.4 kg (50th percentile, P_{50}), height 88 cm (P_{75}) and head circumference 47 cm (P_{50}). There was a healing laceration over the right forehead, extensive scars on her tongue and lower lip and missing front teeth. During a period of hyperactivity, no sweating was

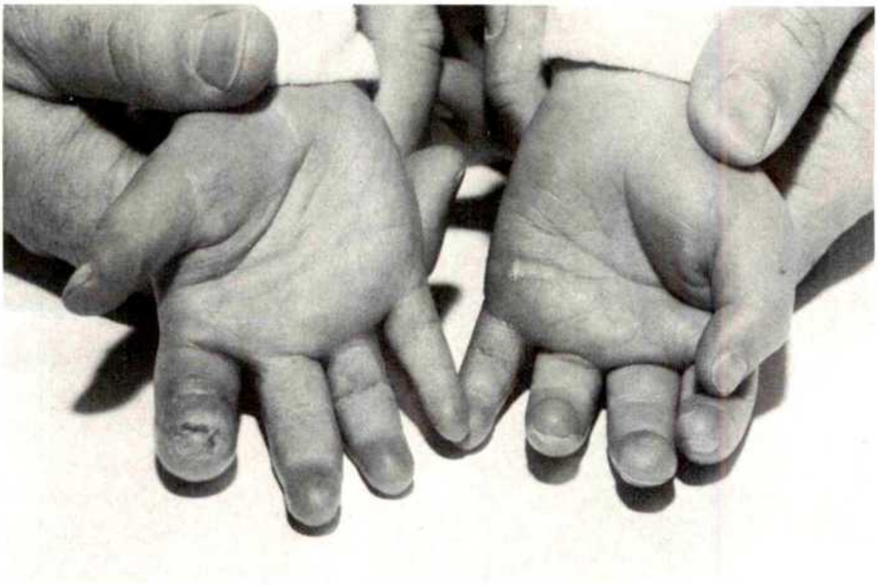

FIG. 1. *Case 1*, showing severely mutilated right index finger.

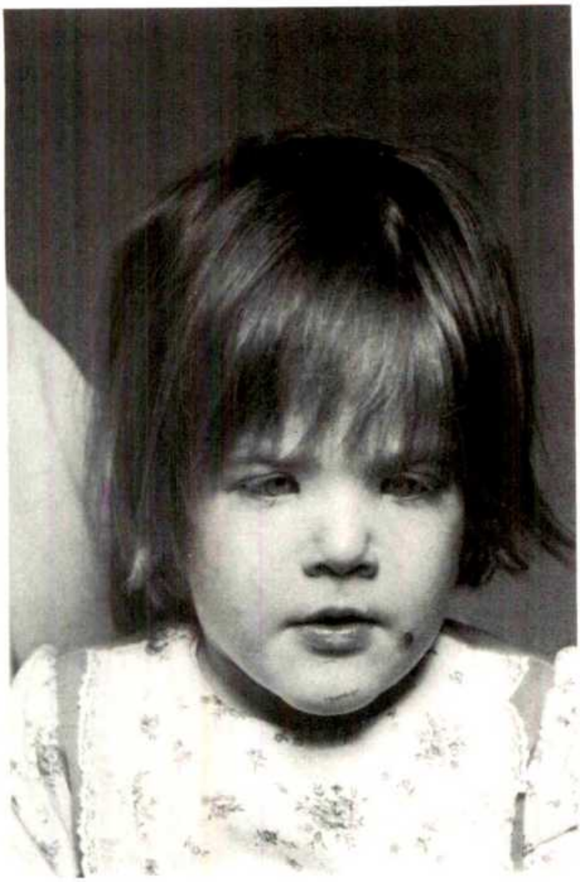

FIG. 2. *Case 1*, showing scar sustained from poking a pencil through her cheek.

apparent. Observation during play did not reveal weakness but she appeared clumsy. The tendon reflexes, at least at the knees, were normal. When touched, she responded by turning her head. When an ice block was applied to her leg or arm she turned to look but allowed it to remain. She did not object or cry out with a strong pin-prick or compression of the Achilles tendons. Although pain reaction from a pin-prick over her face and trunk was less than normal, she could easily be made to withdraw or cry. The skin of the limbs and trunk was excessively dry, as in someone who does not sweat.

Nerve conduction and EMG. The values for motor conduction velocity (MNCV) and distal latency in the ulnar and peroneal nerves and the amplitude of the evoked muscle action potentials were normal (Table 1). Evoked sensory nerve action potentials were also normal. No abnormalities of motor units in hand, thigh and leg muscles were found by needle electromyography. The insertion and probing of the needle during electromyography did not produce any evidence of discomfort. No somatosensory evoked responses could be recorded over the spine from tibial nerve stimulation. Low amplitude, dispersed, delayed responses were recorded from the scalp only with bilateral stimulation.

Laboratory investigations. Routine haematological and biochemical tests were normal. The following determinations were also normal: urinalysis, serum thyroxin,

TABLE 1. NERVE CONDUCTION AND EMG

			Motor studies									*Sensory studies*					
		Age (yr)/	*Ulnar*			*Median*			*Peroneal*			*Median*			*Sural*		*Needle*
Case	*Family*	*sex*	*Amp.**	*CV*	*DL*	*Amp.*	*CV*	*DL*	*Amp.*	*CV*	*DL*	*Amp.*	*CV*	*DL*	*Amp.*	*DL*	*EMG*
1		2/F	5.5	48	1.9	—	—	—	3.5	47	3.5	110	50	1.8	13	2.2	Normal
2		12/M	12.5	57	3.2	6.8	47	4.4	1.5	41	4.0	NR		NR	NR	NR	Polyphasic
	1	29/F	8.0	57	2.5				4.8	54	4.2				5	3.5	Motor unit potentials
3		2/F				6.3	48	2.5	6.0	61	4.7				NR	NR	Normal
	1	31/F	16.0	67	2.5	14.2	63	3.1	5.2	49	3.7	160		1.6	32	3.4	
	2	32/M	11.5	69	2.9				6.5	55	3.9	90		2.1	11	3.6	

* Amp. = amplitude (mV for motor, μV for sensory); DL = distal latency (ms); CV = conduction velocity (m s^{-1}); NR = no response.

quantitative plasma amino acids, serum cholesterol, triglycerides, lipoproteins and phytanic acid, and lymphocyte chromosome karyotype.

Plasma and CSF neuropeptides. Because an abnormality of β-endorphins has been postulated for indifference to pain, we measured various neuropeptides and hormones in plasma and CSF. Plasma values for our patient and for controls (ranges or upper limits of normal in pg/ml were: met-endorphin 32 (10 to 94), ACTH < 15 (< 120), neurotensin 97 (< 150), human pancreatic polypeptide 282 (< 350 pg/ml), substance P < 20 (< 50), vasoactive intestinal polypeptide (VIP) 42 (< 75 pg/ml). CSF values also in pg/ml were: met-enkephalin < 30 (30 to 60), substance P 30 (6 to 30) and VIP 11 (8 to 28).

Compound action potential of sural nerve *in vitro*. Only one point, 10 mm from the stimulating electrode, could be tested owing to the short stature of the patient. The A alpha and C potentials were developed, but the C potential was slightly small. The A delta potential was small with reduction particularly of the lower velocity component (fig. 3).

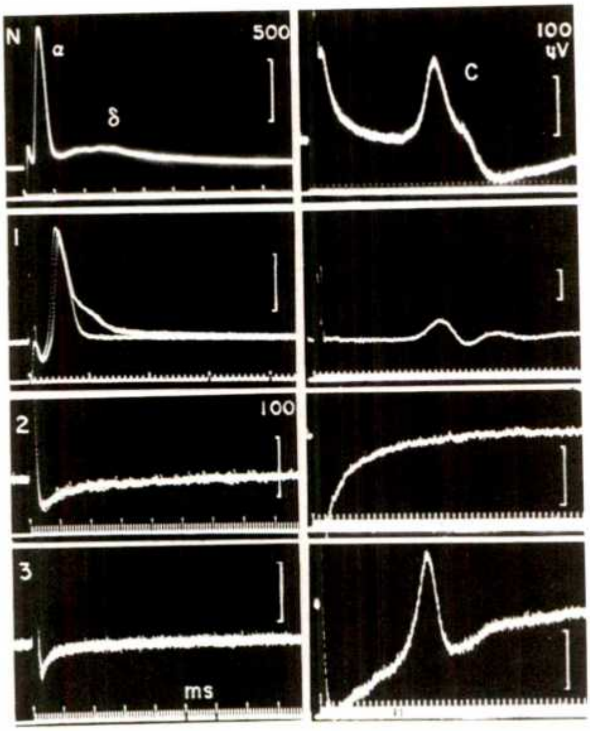

FIG. 3. Compound action potentials of sural nerve fascicle of normal subject (N), aged 23 years, and of Cases 1, 2 and 3 described in the text. The distances from stimulating cathode to recording electrode is 20 mm in N and 15 mm in Cases 1, 2 and 3. The time base for Case 1, A fibres, is expanded to show the small δ potential on the descending limb of the α potential. Responses to three stimuli are shown, one maximal for α fibres only, one maximal for δ fibres and one supramaximal for both. The δ potential is small and probably represents mainly fast conducting δ fibres. The area of the δ potential in Case 1 is less than one-third that in the normal nerve, when measured on the same time base as N. The amplification for Case 1, C fibres is one-half that used for the other C fibre records. In Case 2 only the shock artefact is evident; no α, δ or C potential was detected. In Case 3, only a C potential was detected. Temperature 37° C.

Content and axonal transport of DBH and AChE. These could not be assessed reliably in this case because the amount of tissue available for study was too small. The results, however, did indicate that the DBH activity per unit length of nerve was substantially lower than normal (less than 0.5 pmol/h/mm).

Morphometric and teased fibre evaluation of sural nerve. The transverse fascicular area was 0.32 mm^2 which is smaller than control values (nerves from children 2 yr 2 months, 2 yr 10 months and 3 yr 9 months were 0.51, 0.88 and 0.64 mm^2, respectively. The number of myelinated fibres per nerve was also decreased: 2738 *versus* 7729, 7803 and 8876, respectively.

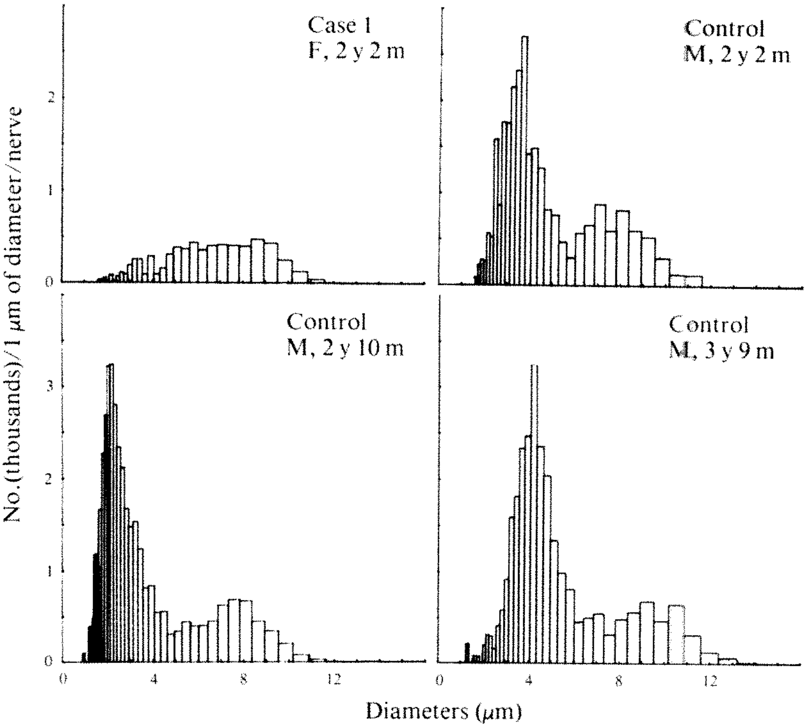

FIG. 4. Diameter histogram of myelinated fibres of sural nerve from Case 1 (*left upper*) and from three controls, as described in text.

The diameter histograms of myelinated fibres of control sural nerve reproducibly yield two diameter peaks. From large to small they consist of a low broad large diameter peak (5 to 12 µm–A alpha fibres), and a tall narrow small diameter peak (1 to 5 µm–A delta fibres). The myelinated fibre diameter histogram of the sural nerve from this child revealed a striking, severe deficit of small diameter fibres (fig. 4). The diameter histograms of unmyelinated fibres generally have one peak at approximately 0.8 µm, but are sometimes bimodal. In our patient's sural nerve,

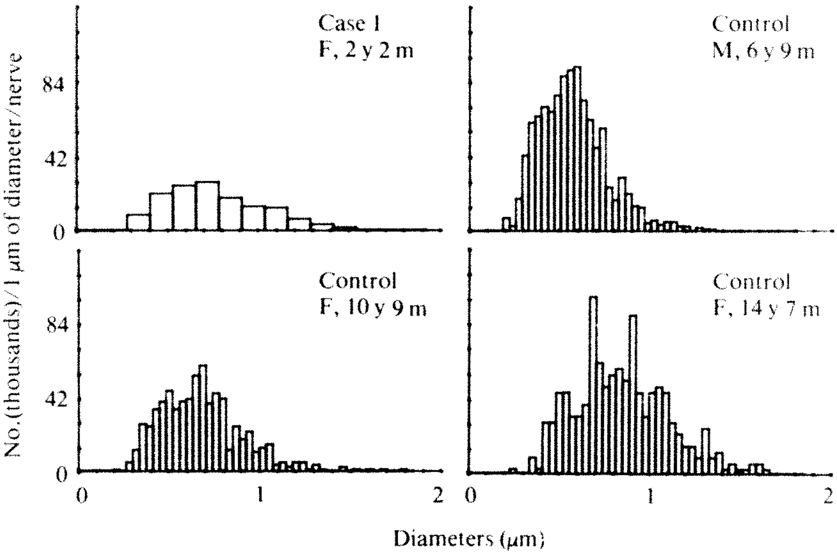

FIG. 5. Diameter histogram of unmyelinated fibres of Case 1 (*left upper*) and from three controls, as described in text.

unmyelinated fibres, although having a normal range of diameters, appeared to be slightly reduced in number (fig. 5).

Semithin and thin transverse sections of the sural nerve and grading of 100 teased fibres provided no evidence of fibre degeneration.

Case 2

Clinical assessments. This 12-year-old boy (fig. 6) with congenital sensory neuropathy, mutilating acropathy of the digits of his hands and feet, severe retinitis pigmentosa and possible mental retardation was the first child of a 16-year-old mother, now gravida 5. There was no history of a similar disorder in the kinship, although there is some question as to paternity. Although the mother does not recall fetal movements, the pregnancy and delivery were otherwise uneventful. At 3 months, the baby was noted by his mother to be abnormal in that he was unable to sit, could not roll over and would not respond when his feet were tickled. Between 6 and 12 months, bite marks on his trunk and fingers and blood on his crib from thumb biting were observed. Medical evaluation at 2 years led to the diagnosis of congenital sensory neuropathy with an abnormality of his eyes, not further clarified. Because of the finger and lip mutilation, his hands and arms were bandaged and even placed in plaster casts, but to no avail. All his teeth were then removed. The acral mutilation and repeated infections and scarring of the lower lip developed between the ages of 2 and 8 years. The threat of self-mutilation—'I will bite off my fingers, if'—may have been used by the child to get his way with his parents. He 'bunnyhopped' around the house until the age of 8 years when he began to walk. His walking was at its best between the ages of 8 and 9 years, but even then was markedly unsteady. He repeately developed ulcers on the plantar surfaces of the great toes and over the front of his knees. When the foot or leg ulcers became infected, he typically developed a fever and would wake up screaming to report a 'drilling' or 'chainsaw-like' pain. Although he had been diagnosed as mentally retarded by psychometric testing, this judgement may need to be reconsidered in the light of his severe sensory and visual impairment, lack of training and obviously extensive knowledge of gospel and rock music, of which he is fond. By 6 years of age he was already having marked difficulty seeing a drinking glass held before him. With crying, tears were seen, but these were reported to be less than those of his siblings. Although generally he experiences no difficulty with micturition at home, he has had several episodes of urinary retention at medical centres.

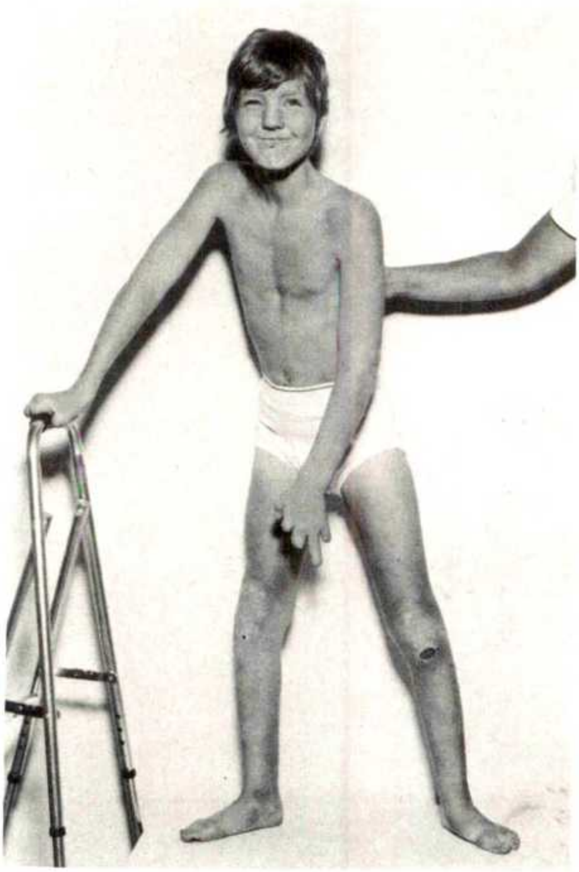

FIG. 6. *Case 2.* This photograph illustrates the severe degree of scarring of the upper and lower lips, the mutilating acropathy of the fingers, ulcers of the knees and neurogenic arthropathy of the knees.

On examination, he was only able to see hand movements. Widespread retinal pigmentation, optic atrophy and nystagmoid movements of near blindness, typical of severe retinitis pigmentosa, were observed. Neurological examination revealed that his muscle strength and bulk were probably normal, but his limb movements appeared uncoordinated, without check and excessive. Tendon reflexes could not be obtained. Sensory loss was essentially complete over his limbs, severely affected over his trunk and less affected over his face and head. Tactile, vibratory, joint position and motion, thermal and nociceptive sensations were all affected.

The skin over his limbs and trunk was dry and parchment-like. Only a little moisture could be felt in his axillae, groins and over his face. Postural hypotension was not found.

Nerve conduction and EMG (Table 1). MNCV was normal in the ulnar nerve, but slightly reduced for the median and peroneal nerves. The values for distal latency were normal, as were the amplitudes of evoked muscle action potentials except for digitorum brevis responses. No sensory nerve action potentials could be recorded from ulnar, median and sural nerves. Needle electromyographic examination of his left biceps brachii and anterior tibial muscles revealed somewhat polyphasic and long motor units.

Laboratory investigations. Routine haematological and biochemical tests were normal. Plasma amino acid concentration and 24 h urinary amino acid excretion were also normal.

Compound action potential of sural nerve *in vitro.* No action potentials were detected.

Content and axonal transport of AChE and DBH. AChE activity of sural nerve was 0.9 nmol/h/mm or 2.1 nmol/h/mg wet weight (8 per cent of control mean). DBH activity of sural nerve was 0.75 pmol/h/mm or 1.8 pmol/h/mg wet weight (2 per cent of normal). It was not possible to measure the average velocity of transport for AChE or DBH because of low enzyme activity.

Morphometric and teased fibre evaluation of sural nerve. The transverse fascicular area was markedly decreased: 0.07 *versus* 0.51, 0.88 and 0.64 mm^2 of the three nerves from young patients serving as controls. The number of myelinated fibres per nerve was 25 (severely decreased). There was a severe reduction of both myelinated and unmyelinated fibres. Nerve strands were generally without myelinated fibres or breakdown products so it was not possible to grade the frequency of the pathological abnormalities of teased fibres.

Kinship evaluation. The patient's mother, now aged 29 years, has no neurological, nerve conduction, electromyographic or sensory abnormalities employing computer assisted testing (Table 2).

TABLE 2. DETECTION THRESHOLD PERCENTILES (%) FOR LEFT FOOT OF RELATIVES OF PATIENTS

		*Touch-pressure**		*Vibration**			
Case/family	*Age(yr)/sex*	*Threshold*	*Pts. Sens*	*Threshold*	*Pts. Sens*	*Thermal heat flow*	*Cool temp change*
2/1	29/F	> 71	9	> 27	9	> 43	> 56
3/1	31/F	> 50	9	> 29	9	> 37	> 50
3/2	32/M	> 73	9	> 98	8 (> 98)	> 44	> 70
				> 75	9		

* Computer assisted sensory examination (System III)

Case 3

Clinical assessment. This 2½-year-old girl, an only child of unrelated American parents without a family history of similar disorder, was investigated for congenital insensitivity to pain and retarded neuromuscular development. Apart from dysuria, for which only local treatment was used, the mother had not had an x-ray, or ingested drugs or chemicals during the pregnancy. Delivery was premature

(32 weeks) and the birth weight was 2.2 kg. Intermittent respiratory support was provided for ten days. Because the infant was 'floppy' and would not suckle, feeding was provided intially by gavage, then by medicine dropper and, later, by teaspoon. By 2 months, dysautonomia was considered because of poor development and lack of a pain response to venepuncture. Motor development, but not mental development, was delayed. Sitting unaided was delayed to 2 years. By 2½ years she could roll from side to side and was beginning to move from place to place from a seated position. Her parents report that she does not seem to know where her limbs are in space. Feeding remains difficult because food placed into her mouth may stay there unchewed and not be moved to the pharynx. A mirror is being used to show her how to handle food orally. She appears to be of at least normal intelligence as she already speaks in sentences. Regarding pain insensitivity, her parents relate that she has bitten her tongue, cheeks and fingers without crying and several corneal erosions have developed. With these, she has not reacted as if in pain. With respect to autonomic function, her mother reports decreased, but not absent, overflow tears and intermittent, unexplained sweating on the top of her head and forehead, but no overheating in warm weather. Control of micturition has been satisfactory, but severe constipation to the point of impaction is a recurring problem.

She often keeps her mouth slightly open and saliva bubbles out. Her height is 82 cm, her weight is 9.5 kg and her head circumference is 47 cm. The muscles of her limbs are well developed but she has mild bilateral pes cavus Even when she is supported under her arms, she does not bear any weight on her legs. However, this is obviously not due to weakness as she can move her legs forcibly. With her eyes open, she can grasp a target, such as a hand held before her, with only a slight degree of ataxia. With her eyes closed, she cannot find the target. Tendon and corneal reflexes are absent. There is a slight corneal abrasion on the right eye. Generally, she does not respond to tactile or nociceptive stimuli over her limbs and trunk. There is a slight, although severely diminished, response to nociceptive stimuli (pinprick and pinch) over her face and scalp.

Laboratory investigations. Routine haematological and biochemical tests were normal. No chromosomal karyotype abnormalities or amino aciduria were found. Serum β-endorphin was 30 pg/ml and CSF β-endorphin was 28/pg/ml.

Nerve conduction and EMG (Table 1). MNCV in the median and peroneal nerves was normal, as were the distal latencies and the amplitude of evoked muscle action potentials. In contrast, no response could be obtained from stimulating afferent fibres of median and sural nerves. Needle electromyography of the left biceps brachii, first dorsal interosseus, anterior tibial and medial hamstring muscles was without abnormality. Only low amplitude somatosensory evoked potentials of normal latency were recorded over the spine from tibial nerve stimulation. No response could be recorded from the scalp.

Compound action potential of the sural nerve *in vitro*. A alpha and delta potentials were not detected. A C potential of normal amplitude was recorded (fig. 3).

Content and axonal flow of AChE and DBH. Sural nerve AChE activity was 3.9 nmol/h/mm or 9.5 nmol/h/mg wet weight (36 per cent of control mean). Apparent average velocity of transport was 1.9 mm/h ($\geq$ normal). Sural nerve DBH activity was 1.8 pmol/h/mm or 4.2 pmol/mg wet weight (4 per cent of normal). Velocity of transport was not measurable because of low enzyme activity.

Morphometric and teased fibre evaluation of sural nerve. The total fascicular area was abnormally small (0.06 mm^2 *versus* 0.51, 0.88 and 0.64 mm^2 of controls). The total number of myelinated nerve fibres was 4 (severely abnormal). No myelinated fibre breakdown products were encountered in semithin and thin sections and in teased fibres.

Kinship evaluation. The father and mother, now aged 32 and 31 years, respectively, were examined but no abnormality of the neurological, nerve conduction, EMG or computer assisted sensory assessment was found (Table 2).

DISCUSSION

Sensory loss, as a result of disease of primary afferent neurons (or their axons) may be associated with various symptoms depending, possibly amongst other factors, on the population of neurons (or axons) affected (Dyck and Lambert, 1969; Dyck *et al.*, 1971). Thus selective degeneration of large diameter deep and cutaneous afferent fibres, as found in Friedreich's ataxia and other spinocerebellar degenerations, is associated with loss of low threshold mechanoreception, discrimination of shape and texture and coordinated movement. These patients do not experience such 'positive sensory symptoms' as 'burning', 'lancinating pains' or 'prickling' and are not predisposed to tissue mutilation. Selective absence or degeneration of small fibres (afferent and autonomic), on the other hand, as encountered in various hereditary sensory neuropathies, is associated with a variety of autonomic symptoms, raised detection thresholds of nociception and thermal discrimination and, in some cases, 'positive sensory symptoms' and tissue complications (Dyck, 1983). Although large diameter fibres may also be involved, these patients do not have the severe ataxia of the former group, either because muscle and joint afferents are spared or because the cerebellum is unaffected.

Early accounts of patients having the second category of sensory dysfunction used nomenclature that emphasized tissue complications, for example inherited perforating ulcers (Hicks, 1922), mutilating acropathy (Thévenard, 1942) and inherited whitlows (Morvan, 1883, 1889; Joffroy and Achard, 1890; Ogryzlo, 1946). In other cases, the disorder was named after the author describing the disorder, as in Morvan's syndrome (1883, 1889). Still other names for these disorders emphasized the nature of the sensory loss, for example congenital indifference (Arbuse *et al.*, 1949; Boyd and Nie, 1949) or congenital insensitivity to pain (McMurray, 1950; Baxter and Olszewski, 1960; Feindel, 1953). Initially, syringomyelia was thought to account for the sensory loss in the dominantly inherited variety (Thévenard and Coste, 1935; Van Epps and Kerr, 1940), but at post-mortem examination no cavity was found (Jughenn *et al.*, 1949) and degeneration of sensory neurons was demonstrated (Denny-Brown, 1951).

Among the examples of inherited and congenital HSAN (which we also assume to be usually inherited), there are differences in mode of inheritance, age at onset, course, symptoms, populations of neurons (or axons) affected and, presumably, underlying biochemical mechanisms which may be used for classification (Dyck and Ohta, 1975). Type I, which is dominantly inherited, may encompass cases described as hereditary perforating ulcers of the feet (Hicks, 1922), familial mutilating ulcerative acropathy (Thèvenard, 1942; DeJong, 1967), hereditary lumbosacral syringomyelia (Thèvenard and Coste, 1935; Van Epps and Kerr, 1940), familial neurogenic acro-osteolysis (Giacci, 1952), hereditary sensory neuropathy or hereditary sensory radicular neuropathy (Denny-Brown, 1951), hereditary sensory neuropathy with peroneal muscular atrophy (England and Denny-Brown, 1952; Dyck *et al.*, 1965) and acrodystrophic neuropathy (Spillane and Wells, 1969). Types II, III and IV are congenital sensory neuropathies and are probably recessively inherited. Type II (Dyck, 1966; Haddow *et al.*, 1970; Ohta *et al.*, 1973; Kondo and Horikawa, 1974) probably includes cases designated as Morvan's syndrome (Joffroy and Achard, 1890; Head, 1903; Cruchet *et al.*, 1920; Ogryzlo, 1946), hereditary sensory neuropathy (Heller and Robb, 1955; Dyck *et al.*, 1965; Ohta *et al.*, 1973) and possibly some of the patients described as congenital insensitivity to pain (or analgesia), or indifference to pain. Type III is usually referred to as familial dysautonomia (Riley and Moore, 1966; Brunt and McKusick, 1970; Pearson and Pytel, 1978). Because sensory symptoms result in the major disability and because of its similarity to other types of congenital HSAN, familial dysautonomia is reasonably classified with them. Type IV has been described as congenital insensitivity to pain with anhidrosis (Swanson, 1965), congenital sensory neuropathy with anhidrosis (Pinsky and DiGeorge, 1966), syndrome of the neural crest (Brown and Podosin, 1966) and HSN Type IV (Dyck and Ohta, 1975; Goebel *et al.*, 1980).

It is less clear whether the cases with asymbolia for pain (Schilder and Stengel, 1931), congenital indifference to pain (Arbuse *et al.*, 1949; Boyd and Nie, 1949), congenital pure analgesia (Dearborn, 1932) and congenital universal insensitivity to pain (McMurray, 1950; Feindel, 1953; Baxter and Olszewski, 1960) should be included with HSAN. Characteristically, these patients did not experience pain anywhere over their bodies from needle-prick or injury, but could recognize the point from the head of a pin, had no physiological responses to noxious stimuli, no evidence of neurological abnormality and biopsy and post-mortem examination did not disclose a structural abnormality of nerve, spinal cord or brain. On the other hand, their nerves were not studied by the definitive methods now available. Thus abnormalities such as described here or in the type IV disorder might not have been detected.

Our finding of a neuropathic disorder, despite preserved reflexes and normal nerve conduction, requires emphasis. In addition to HSAN types IV and V, such findings have been detected in Fabry's disease (Ohnishi and Dyck, 1974) and at the early stages in some cases of inherited amyloidosis (Dyck and Lambert, 1968).

The three patients presented here appear to have different types of congenital (possibly inherited) sensory and dysautonomic neuropathies. Although she is too young for somatic sensation to be assessed in detail, the first patient appears to resemble the historic cases identified as congenital universal insensitivity or indifference to pain. She responds to tactile stimuli, is generally insensitive to pain, has preserved tendon reflexes, normal motor and especially afferent nerve conduction, and in transverse sections of sural nerve both small and large myelinated fibres and unmyelinated fibres are present. With a more detailed assessment, however, we were able to demonstrate an abnormality of the sudomotor response, of sural nerve DBH content and a selective, virtually complete, absence of small myelinated (A delta) afferent fibres. With this information, we must assume that her severe nociceptive abnormality is related either to the absence of small myelinated fibres, absence of unmyelinated nociceptive fibres, an abnormality of central nociceptive pathways or functional nociceptive anomalies. Complete loss of nociception as the result of absence of A delta fibres alone would not be expected. Therefore, it is assumed that nociceptive unmyelinated fibres, central pathways or physiological dysfunction, must also be involved. Since, in addition, we observed a small reduction in the number of unmyelinated fibres, it may be that the clinical findings can be accounted for by absence of nociceptive fibres in A delta and dorsal root C fibres. Irrespective of the structural and pharmacological basis of the nociceptive loss, we have provided unequivocal evidence of a peripheral nerve abnormality.

A previous case reported by Low and coworkers (1978) resembles our first case. Their 6-year-old patient had a congenital selective nociceptive defect affecting the extremities in particular. They reported a selective, severe decrease in small myelinated fibres. Although the number of unmyelinated fibres was reported as normal, this might have been slightly low if control values from age-matched cases had been used. Muscle strength was normal, tendon reflexes were intact and mechanoreception was preserved. Pain and thermal sensation was abnormal in the limbs. We would, therefore, tentatively classify these cases (Low's case and our Case 1) as the fifth type of HSAN.

Our second patient also has an insensitivity to pain but the congenital peripheral nerve abnormality affects mostly afferent fibre groups, all types of sensation and the entire body. Tendon reflexes are absent and afferent nerve potentials cannot be evoked. Cutaneous nerves are excessively small and show, in addition to an almost complete absence of myelinated fibres, a decrease in the number of unmyelinated fibres. This is typical of patients with HSAN II. Because deep nociception and tendon reflexes are affected, we assume involvement not only of cutaneous fibres but also of deep afferents. This patient appears, therefore, to be more severely affected than those of our Quebec kinship (Ohta *et al.*, 1973), particularly by a greater involvement of muscle and joint afferents. This picture is more like the congenital pansensory neuropathy described by Adams *et al.* (1973). Our Case 2 has, however, the additional feature of retinitis pigmentosa.

Our third patient has many of the laboratory features of HSN II but displays more widespread and severe involvement, especially to cranial, truncal and deep structures. In addition, the severity of dysautonomic symptoms is greater than usual with HSN II.

Because all patients with the five types of hereditary sensory neuropathy have autonomic symptoms, it seems reasonable to recognize this involvement by designating them as hereditary sensory and autonomic neuropathies (HSAN).

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CALLOSAL APRAXIA

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SUMMARY

A 43-year-old woman suffered a spontaneous corpus callosum disconnection, resulting in apraxia and apraxic agraphia confined to the left hand. She initially had a functionally total callosal disconnection. With time, the splenium of the corpus callosum became functional, and a computerized tomographic scan performed five months after the onset showed infarction of only the body of the corpus callosum. Concomitant with this improvement in callosal function, the apraxia changed from ideational (loss of the concept of skilled movements) to classic ideomotor apraxia. A temporal analysis of this case provided support for Liepmann's (Liepmann, 1900; Liepmann and Maas, 1907) hypothesis that there is a centre for visuokinaesthetic (space-time) engrams in the left hemisphere of right-handed patients that controls skilled motor acts in either hand. This patient's recovery also allowed us a better understanding of the mechanisms underlying various types of apraxia.

INTRODUCTION

Apraxia is a disorder in the execution of learned skilled movement that cannot be explained by lack of comprehension or by inattention, sensory loss, weakness, ataxia or basal ganglia disorder. Liepmann (1900) was the first to study apraxia systematically. He first described a government official with apraxia in both arms, the impairment being much greater on the right side than on the left. Liepmann used this case to show that impaired motor execution could exist with intact language comprehension.

In 1907 Liepmann and Maas described a second case, that of Ochs, a 70-year-old carpenter who had transcortical motor aphasia with apraxia and agraphia of the left arm and with right hemiplegia. His apraxic (left) hand did not improve with imitation or actual object usage, and the left hand agraphia did not improve with use of anagram letters. Post-mortem examination showed a left anterior cerebral artery infarction with damage extending from the first frontal convolution through the white matter to the paracentral lobule with destruction of the anterior two-thirds of the corpus callosum. There was also a lesion of the left pons, which explained the right hemiplegia. Liepmann and Maas postulated that engrams for skilled movements are lateralized and in right-handers these engrams are in the left hemisphere.

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These engrams were called *space-time engrams* by Liepmann in 1920 (*see* Brown, 1972) and *visuokinesthetic motor engrams* by Heilman (1979). Heilman (1979) proposed that these engrams were stored in the parietal lobe.

These engrams are needed to perform learned skilled acts. Depending upon the nature of the act, specific body parts must be placed in certain spatial positions. The spatial positions assumed by the relevant body part depend not only on the nature of the act but also on the position and size of an external object with which the body parts must interact if an external object is present. Unlike static postures, skilled acts require orderly sequential changes in the spatial positions of the body parts over time. These space-time engrams command the motor systems to adopt the appropriate spatial positions of the relevant body parts over time. Because these engrams for skilled movement are lateralized, Liepmann and Maas thought that a lesion of the corpus callosum would prevent the space-time engrams in the left hemisphere from reaching the right sensorimotor area necessary to carry out the skilled act with the left hand, thereby inducing apraxia.

Since Broca's (1865) description of eight aphasic right-handed patients who had left hemisphere lesions, it has been well established that in right-handers the left hemisphere mediates language. Liepmann and Maas (1907) recognized that a callosal lesion therefore disconnects the motor area in the right hemisphere from the language-dominant left hemisphere. If a right-handed patient with a callosal lesion had a language-motor disconnection, the patient should be unable either to perform skilled movements to command or to write with the left hand. If, however, as Liepmann and Maas suggested, right-handed patients also have space-time or visuokinaesthetic engrams in their left hemisphere, a callosal lesion would not only disconnect language from the right hemisphere but would also disconnect the left hemisphere space-time motor engrams from the right hemisphere motor areas. Such patients should be unable to carry out commands with their left hand and also fail to imitate and use actual objects correctly.

Since Liepmann and Maas's report, there has been little support for this hypothesis. Geschwind and Kaplan (1962) described a patient with a left hemisphere glioblastoma and a postoperative left anterior cerebral artery infarction that had caused destruction of the anterior four-fifths of the corpus callosum. That patient could not follow commands with his left hand but could imitate and use actual objects. He was agraphic in the left hand and could not type or use anagram letters with the left hand but performed flawlessly with his right hand. He followed commands with his right hand but not with his left. He failed when asked to draw with his right hand an object placed in his left hand. The aphasic agraphia was interpreted as disconnection of the right hemisphere from left hemisphere speech areas, and the apraxic difficulties were attributed to having stimulus (verbal or nonverbal) and response separated across the hemispheres. Geschwind (1975) concluded that in the verbal condition many cases of apraxia are caused by a verbal-pyramidal system disconnection, intrahemispherically or interhemispherically. For example, intrahemispherically, a left premotor lesion or a lesion disconnecting

Wernicke's area from the left premotor region would cause the patient to be unable to perform distal skilled movements with either hand in response to a command. Interhemispherically, a callosal lesion would disconnect the left hemisphere from right premotor cortex and cause apraxia isolated to the left hand. Clumsily performed attempts at skilled acts were thought to be under extrapyramidal control. This could explain the dysfunction in Geschwind and Kaplan's patient, who could imitate and use objects correctly, because nonverbal cues could presumably activate the right pyramidal system. Their conclusion could not explain the frequently observed impairment of praxis for imitation. However, these investigators also agreed with Liepmann and Maas (1907) and accepted the postulate that the left hemisphere in right-handed persons may dominate motor skills and that their callosal patient could be the exception. Further investigation (Heilman *et al.*, 1973, 1974) showed that dominance for language and dominance for skilled motor acts are separable. Therefore, a callosal disconnection may induce a verbal motor disconnection alone or disconnect language and space-time engrams from right hemisphere motor areas.

Gazzaniga *et al.* (1967) observed that relatively pure surgically induced callosal lesions caused mild disturbance of praxis, limited to fine differential movements of thumb and fingers. They concluded that each hemisphere exerts control over homolateral and contralateral limbs and that previous cases of severe apraxia following a callosal lesion were secondary to extracallosal damage. Limiting the surgery to the corpus callosum and hippocampal commissure and operating in two stages has reduced the 'acute disconnection syndrome'—apraxia of the left limbs, mutism, apathy, confusion and infantile behaviour (Wilson *et al.*, 1982). Furthermore, improvement in praxis was thought to be secondary to more acquisition of homolateral control with time (LeDoux *et al.*, 1978).

Recently we had the opportunity to examine a patient with an acute naturally occurring callosal lesion who, unlike the patient of Geschwind and Kaplan (1962), had severe apraxia with imitation and object usage, thereby providing support for Liepmann's hypothesis. This patient also had other signs and symptoms that may help to elucidate the neuropsychological mechanisms underlying other varieties of apraxia and the mechanisms underlying apraxic agraphia.

CASE REPORT

A 43-year-old right-handed woman without history of previous illness, on September 5, 1981, suddenly developed severe headache followed by vomiting, mutism and inability to stand. She was admitted to the University of Florida's Shands Teaching Hospital where examination showed neck stiffness and a blood pressure of 142/98. Initially she had no spontaneous speech but repeated complex phrases normally. She followed verbal commands by pointing with her right hand, and could follow written commands presented in her right visual field but not in her left visual field. She could perform a finger snap flawlessly and a coin flip to command with her right hand but not with her left hand. Her cranial nerves were normal. She orientated to visual stimuli in both visual fields with no evidence of hemianopia. She had bilateral weakness of her legs, the right being weaker than the left. Strength in her arms was normal.

A computerized tomogram (CT) showed a haemorrhage in the region of the corpus callosum, extending from the genu to the splenium. Coronal reconstruction showed this to be above the corpus callosum. The following day cerebral angiography did not reveal the cause of the haemorrhage but showed severe spasm of both anterior cerebral arteries.

Examination two days after admission showed the patient to be alert but severely hypokinetic with a long latency between any stimulus and response. She orientated to both sides equally. She was mute, except for use of a rare single word. After a long latency, she could repeat phrases such as 'no ifs, ands or buts'. She comprehended simple pointing commands such as 'point at your doctor, point to the television'. She comprehended simple written sentences and named objects without difficulty. On praxis testing, with her right hand she pantomimed flawlessly to commands like 'comb your hair'. Asked to pantomime with her left hand to command, she would extend her fingers, look at them and then flex and extend them slowly. During her performance she had a bewildered expression on her face. She did not improve with imitation or with the use of actual objects. She could write single words with her right hand but not with her left.

She was thought to have a callosal disconnection syndrome, a severe transcortical motor aphasia and generalized hypokinesia from supplementary motor area involvement, and proximal leg weakness from medial motor cortex ischaemia, all caused by anterior cerebral artery spasm.

Three days after the haemorrhage she was noted to be orientating more to her left than to her right. On bilateral simultaneous facial tactile stimulation, she could demonstrate that both sides of her face were touched by holding up two fingers. In spite of spontaneous orientating to her left, she failed to report all left limb tactile stimuli when stimulated either unilaterally or bilaterally. She continued exhibiting transcortical motor aphasia and was found to be hemialexic, reading 'boat' when presented with the word *houseboat* and 'house' when presented with the word *doghouse*. Because she spontaneously orientated more to her left than to her right, she did not have left side neglect; this, therefore, could not explain her hemialexia. When blindfolded she could not name objects placed in her left hand. She could, however, pick the object from a multiple choice array (four foils and the correct object). Unlike patients with astereognosis, she systematically explored the surface of large and of small objects, which she manipulated with normal dexterity with her left hand. She wrote single words with her right hand but not with her left. Her severe isolated left hand apraxia persisted. In spite of her inability to perform the simplest pantomimed act to command, to imitate or to use an actual object with her left hand, she would more often use the left hand rather than the right to scratch her head, wipe her brow, scratch her nose or rub her eye. These acts were also performed in a normal fashion without any evidence of clumsiness. She made fine, precise and well-coordinated finger movements. She could pick up small, thin coins from a table top by using her left thumb and forefinger in the normal pincher-like grasp that is often lost with pyramidal disease (Brinkman and Kuypers, 1973). There was never any evidence of exprapyramidal dysfunction or ataxia.

On the fifth day after the haemorrhage, she fluctuated from transcortical motor aphasia to almost normal linguistic ability. She could write with her right hand but not with her left hand and looked at the pen as if she did not know what to do with it.

By the ninth day she continued to initiate speech slowly. She was mildly dysarthric, but repetition was thought to be no better than was spontaneous speech. She still could not pantomime or imitate with the left hand. With actual objects there was some movement present in the left hand but nothing approximating to the correct movement. In palpating objects for identification with the left hand, she would simultaneously make movements with her right hand as if she were manipulating the object. She continued to show no buccofacial apraxia and when asked to 'blow a kiss' using her left hand, she raised the left hand but did not coordinate it with her mouth or with blowing. Nevertheless, this association with buccofacial praxis appeared to improve her left hand praxis slightly.

She had difficulty naming affective expression, pointing to a named facial affect like 'point to the happy face', and deciding whether two faces showed the same or a different emotion. When she was read sentences and asked to point to one of the four pictures depicting the semantic message of the sentence, she performed flawlessly. When read the same sentence in affective intonations (for example, happy, sad, angry or indifferent), she was unable, either by naming or pointing, to identify the affect of the speaker. She seemed puzzled, and after a long latency stated, 'I am confused . . . this is confusing'. She also could not repeat affective intonation produced by the examiner. Once again, she appeared puzzled and stated, 'this is confusing'. In contrast, she flawlessly repeated lengthy and syntactically complex sentences without affective intonation. In her spontaneous speech she appropriately produced happy intonation.

By the twenty-fifth day she had consistently regained the ability to name small objects placed in her left hand. She had no drift of outstretched extremities or pseudoathetosis of her fingers. Clinical examination showed that position and vibration sense of the left fingers were normal. Strength and tone of her arms remained normal and without tremor or ataxia in performing distal movements. On praxis testing, when asked to pantomime to command, she would still look at her left hand in a bewildered fashion. Although the imitated act was poorly performed because of spatiotemporal movement errors, the intent of the act was recognized as appropriate. She improved further in the use of actual objects but continued to have severe spatiotemporal impairment (for instance, with a key in her hand she moved it slowly forward but then stared at it without making a turning movement with her wrist). With a hammer she made a few slow, large-amplitude swings to and fro but not in an up-and-down direction. She initiated language after a short latency and had excellent comprehension and fluent output. The strength in her lower limbs had improved, and she could stand with assistance. She complained spontaneously that her two hands 'fight each other'. For example, when she held an envelope, each hand independently and simultaneously tried to release and hold, so that she would tug at the envelope sometimes for as long as ten minutes before saying 'the hell with it' and throwing it away with her right hand. She stated 'I just can't make my left hand do what it is supposed to'.

Forty-four days after the ictus, examination showed that she was alert and orientated, with normal comprehension and language output. She could write normally with her right hand. Writing with her left hand produced an illegible scrawl (fig. 1). When writing the alphabet with her left hand, she also produced only a few recognizable letters, but when copying the alphabet, although it was done with great effort, she showed definite improvement. In spite of this agraphia, she could type normal sentences using her left hand (fig. 1). With her left hand she slavishly copied a cube that had good visuospatial relationships; with her right hand it was done with motoric ease but was visuospatially incorrect. Praxis testing showed that in pantomime to command, she now showed the correct intent of actions although she remained severely apraxic. Proximal left arm movements were performed perfectly (for example, using her left arm as if it were a wing, pulling a chair from under a table). When she attempted to pantomine throwing a ball to command, the proximal movements were normal but hand release was severely abnormal. She was unable to pantomime correctly using a comb, key or hammer, or to flip a coin and improved only minimally with imitation. She improved much more using the actual objects; her movements, however, remained apraxic.

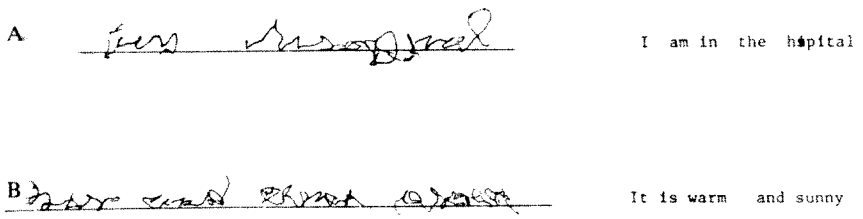

A
I am in the h$pital
B
It is warm and sunny

FIG. 1. A, on the left is an attempt by the patient to write a sentence with her left hand in response to 'Where are you?' On the right is her typewritten response using her left hand. The patient is not a skilled typist, and the error in *hospital* was typographical. B, on the left is an attempt to write a sentence with her left hand in response to 'What kind of weather are we having today?' On the right is her typewritten response with her left hand.

Her family stated that her generally happy premorbid mood was unchanged, but that when she saw something sad on television, she would cry, which she would not have done previously. The family kept records of some of the interesting behaviour that demonstrated the lack of cooperation between her left and her right hands. One day she decided to wear a blouse; she took one out of the closet with her left hand and a separate one with the right hand. She then put her left arm in one blouse and her right arm in the other. The two hands never helped each other; the left hand pulled the right blouse off, and the right arm put the blouse back on, whereupon the left pulled it off once again. Her daughter then intervened. On another occasion she opened a cabinet with her left hand and with her right hand reached into the cabinet only to have her left hand close the door on her right arm. On still another occasion she put her right arm half-way into a sweater and then her left hand started taking the sweater off. She repeated this twice. Her left hand then put the sweater on the floor, her right hand picked it up and started to put it on, whereupon the left arm again started to take if off.

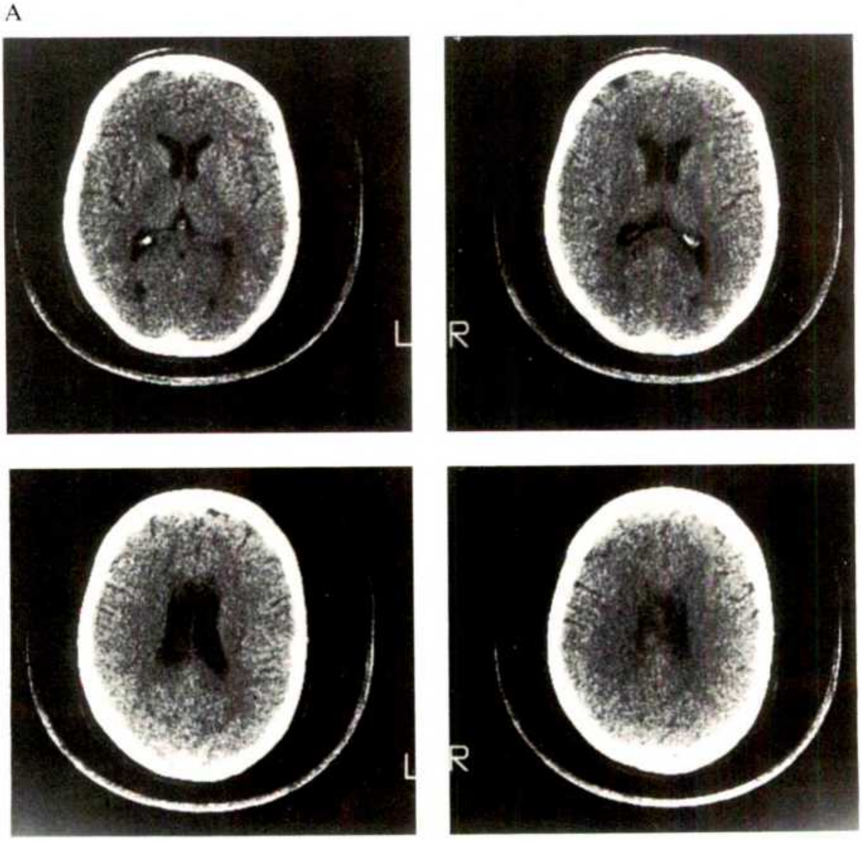
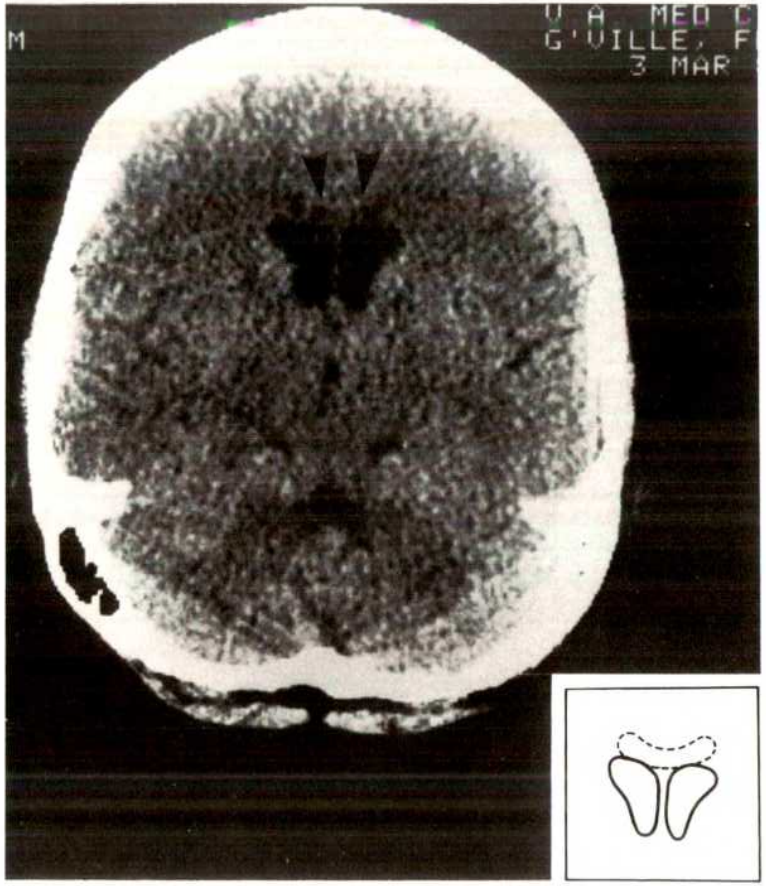
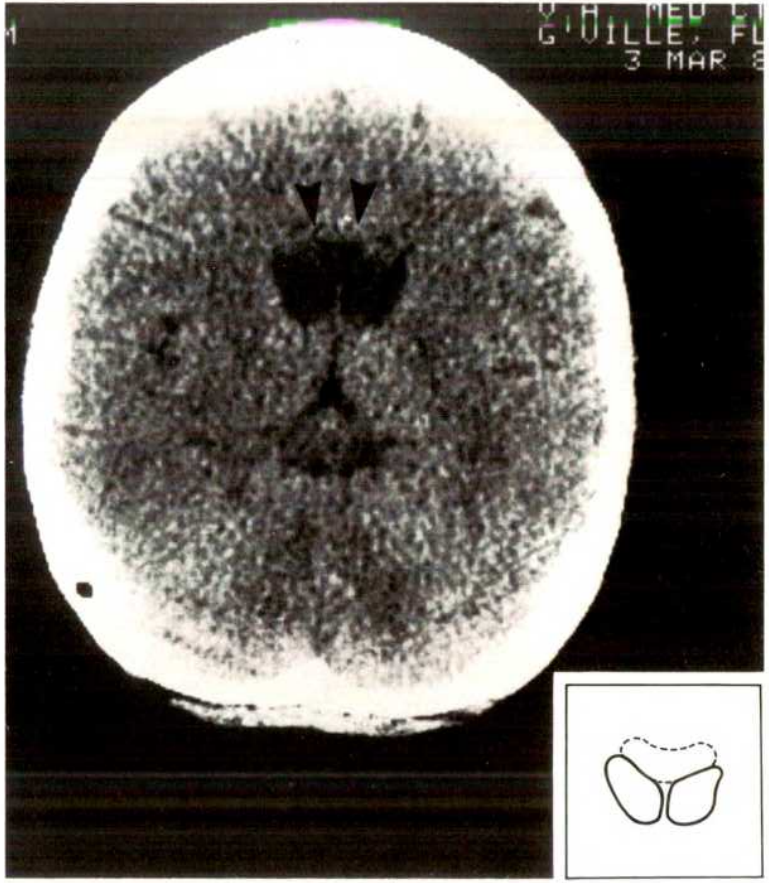


FIG. 2. Computerized tomographic scans five months after the ictus. A, horizontal sections showing infarction of the body of the corpus callosum. B, 35 deg coronal section showing infarction at the junction of the genu and body of the corpus callosum. The insert shows the relationship between the infarction and the ventricles diagrammatically. C, 35 deg coronal section showing infarction of the body of the corpus callosum. This insert also shows the relationship between the infarction and ventricles. D (*overleaf*), artist's reconstruction of callosal infarction.

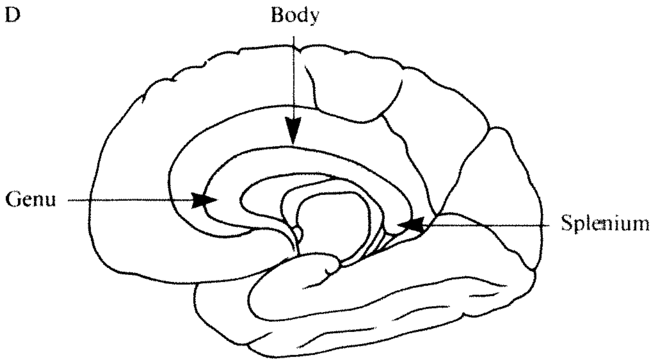
B



C



D



Five months post-onset, she continued to have severe ideomotor apraxia (*see* Table) confined to the left arm. When she attempted to perform a pantomime to command, the intent of her actions was clearly recognizable although severely apraxic. She improved with imitation and further improved with actual object usage although remaining apraxic. The results of her neurological examination were otherwise normal. Horizontal and 35 deg coronal CT scans were sent to Dr William Scott (New and Scott, 1975). Without providing him with clinical details, we asked him to determine all abnormalities and their exact anatomical extent. His 'blind' interpretation was of an extensive infarction of the body of the corpus callosum (fig. 2A–D). The most anterior extent of the infarction was at the junction of the genu and body. The posterior one-fourth to one-fifth of the body and all of the splenium were intact. There was no cortical involvement, including supplementary and cingulate cortex.

TABLE. DISTINGUISHING FEATURES OF VARIOUS TYPES OF APRAXIA

Type of apraxia	*Pantomime to command*	*Imitation*	*Object usage*
Ideational	Does not demonstrate correct intent. Loss of movement concept	Same as to command	Same as to command
Verbal-motor disconnection	Same as ideational	Correct	Correct
Ideomotor	Correct intent but spatiotemporal errors	Improves over command but spatiotemporal errors may persist	Improves over imitation but spatiotemporal errors may persist
Verbal-motor disconnection plus ideomotor	Same as ideational	Shows correct intent. Improves over command but spatiotemporal errors may persist	Improves over imitation but spatiotemporal errors may persist

DISCUSSION

This is a case of spontaneous disconnection of the body of the corpus callosum caused by haemorrhage-induced spasm of the anterior cerebral arteries resulting in infarction. During the patient's hospital course she showed many of the signs and symptoms that have been previously described for surgical disruptions of the corpus callosum. The major focus of this report, however, is the left side apraxic disorder.

During recovery she has evolved through three types of apraxia (*see* Table): initially she had ideational apraxia, then verbal-motor disconnection with ideomotor apraxia and, finally, severe and lasting ideomotor apraxia. The apraxia was exclusively limited to her left extremities. She could always recognize the appropriate act from multiple similar acts performed by the examiner.

Initially, when asked to pantomime skilled acts with her left hand, she looked at the hand and alternately pronated and supinated it or flexed and extended her fingers. She could not even attempt the requested pantomime. This behaviour resembled that previously described by Heilman (1973). Heilman (1979) postulated that the disorder in his patients was being induced by a verbal-motor disconnection; that is, although they verbally comprehend the command to pantomime, this command will not excite the visuokinaesthetic (space-time) engrams. However, unlike performance of patients who can imitate and use actual objects flawlessly (Heilman, 1973), this patient's performance during imitation or with the actual object was precisely the same as it was to command; initially her performance appeared to be like that described by Liepmann and Maas (1907). Some aphasics with profound comprehension disorders cannot pantomime a skilled act to verbal commands but can perform skilled acts when given the actual objects. These observations suggest that verbal comprehension and knowledge of object use are dissociable. The failure of this patient to use actual objects with her left hand therefore cannot be entirely explained by an inability of her right hemisphere to understand a command (either directly or *via* the corpus callosum). Similarly, although severely apraxic patients with left hemisphere lesions may have difficulty with the spatial and temporal dimensions of their movements when using actual objects, these patients demonstrate that they know the intended use of the objects. Our patient's inability to demonstrate the intended use of an object, or even to attempt using actual objects, cannot therefore be explained by a verbal-motor disconnection or by a disconnection of visuokinaesthetic motor engrams from the right hemisphere motor areas. When she first held objects in her left hand, her performance was as if she had never seen or worked with these objects and did not know their intended use. We therefore suspect that initially there was a conceptual disorder. The disconnected right hemisphere did not know what the object was used for or even that it was to be used. Unfortunately, the term *ideational apraxia* has been used for several disorders (Heilman, 1979). Ideational apraxia perhaps best describes the left-hand performance by this patient. Because the right hand performed normally, the concepts of what objects are used for were not destroyed but were disconnected from the right hemisphere.

At about three weeks after the haemorrhage, the nature of the apraxia in this patient changed. When asked to pantomime, she continued either to supinate and pronate her hand or to flex and extend her fingers. Given objects, she attempted to use them. Although she made clumsy movements that were incorrectly orientated and sequenced in space, it was possible to recognize the correct intent of the movement. This improvement coincided with a return of her ability to name objects in her left visual field and in her left hand. The hemialexia had also resolved. These functions are thought to be mediated by the posterior portions of the corpus callosum. The CT scans showed that the posterior portion of the corpus callosum was spared, and although initially it may not have been anatomically disconnected, it may have been functionally disconnected. This dysfunction improved, allowing posterior callosal interhemispheric communication. Furthermore, it may be that the concepts of what objects are used for reached the right hemisphere *via* the posterior route. There are, however, alternative possibilities. Because use of objects did not change when this patient used her vision during the act, we conclude that visual control of ipsilateral pathways could not account for her improvement with object use. The right hemisphere nevertheless may have gained the ability to recognize the object and conceive its use, or the patient may have been using ipsilateral motor pathways. With regard to the latter postulate, proximal movements can be mediated by ipsilateral pathways more than distal movements (Brinkman and Kuypers, 1973), and our patient was best able to perform proximal movements. Against this ipsilateral postulate is the observation that despite normal dexterity, distal movements were poorly performed, although the intent was clearly appropriate. At this stage her total inability to carry out recognizable gestures and to pantomime with the left hand in response to a command but to demonstrate the correct intent with actual objects suggested that the callosal lesion induced a verbal-motor disconnection. The observations that apraxic motor behaviour (spatiotemporal errors) were also found with imitation and actual use of objects with the left hand, also suggested a disconnection of the visuokinaesthetic motor engrams (space-time engrams) from the right hemisphere.

Approximately seven weeks after the haemorrhage, she was able to pantomime with her left hand in response to a command. Although we could recognize the intent of the pantomime, it was apraxic. Her performance with actual object use and imitation was better than that with pantomime, but remained apraxic. The performance of her left hand now could not be accounted for by a verbal-motor disconnection but appeared to be induced by a disconnection of her visuokinaesthetic motor engrams (space-time engrams) from the motor apparatus that controls the left hand. The patient's performance now appeared to be like that of ideomotor apraxia.

We are unsure how the right hemisphere regained access to language. Although we suspect that it used the posterior portions of the callosum, we cannot rule out that her right hemisphere was now directly comprehending commands.

Our patient also had true apraxic agraphia of the left hand. With her right hand, she wrote normally, but her left hand produced an illegible scrawl. Unlike the patients of Liepmann and Maas (1907) and Geschwind and Kaplan (1962), our patient could type linguistically flawless sentences with her left hand. She could type spontaneously and to dictation. Although the linguistic portion of this task may have been mediated by the right hemisphere, she used functional words, was not asyntactic, used abstract words and therefore was most probably using the left hemisphere. Because she could not write with her left hand but could type supports the postulate that the apraxia was not induced by a verbal-motor disconnection. The patients described by Liepmann and Maas (1907) and by Geschwind and Kaplan (1962) had destruction of the genu of the corpus callosum, which was spared in our patient. Because their patients had left-handed apraxic and aphasic agraphia (could not write with anagram letters) and our patient had only apraxic agraphia (could write with a typewriter), perhaps the genu of the corpus callosum is responsible for transmitting verbal-motor programmes to the right hemisphere and the body of the corpus callosum is responsible for transmitting space-time (visuokinaesthetic) engrams to the right hemisphere.

Two recent cases demonstrated aphasic agraphia of the left hand, without apraxia, caused by lesions of the splenium of the corpus callosum (Sugishita *et al.*, 1980; Gersh and Damasio, 1981). Perhaps linguistic information from Wernicke's area destined for the right hemisphere crosses at the splenium. This linguistic information may be different from the verbal-motor information crossing at the genu, and these different lesions might induce different forms of disconnection aphasic agraphia.

Finally, this patient demonstrates the 'alien hand' sign. Her left hand would act in an uncooperative fashion. This has been thought to be secondary to callosal dysfunction but recently was attributed to damage of the medial frontal cortex, including the supplementary motor area and cingulate gyrus, contralateral to the alien hand (Goldberg *et al.*, 1981). Although the present patient had clinical evidence of medial frontal dysfunction early in her illness, manifested by transcortical aphasia and bilateral leg weakness, she subsequently maintained the alien hand after these problems cleared. Furthermore, at no time did she show grasp reflexes or perseveration. The CT scans did not show abnormalities in the medial cortex. Therefore, our patient's alien hand seems more related to callosal dysfunction than to medial frontal cortex infarction.

Why does our patient's disorder differ from previously described cases of callosal disconnection? Many of the patients who had surgical callosal lesions had prior seizures and brain injury. Either of these dysfunctions may have induced brain reorganization. However, Geschwind and Kaplan's (1962) patient did not have these factors; therefore, the absence of a left-hand ideomotor apraxia cannot be entirely explained by brain reorganization. In right-handers right hemispheric lesions almost never produce apraxia; however, left hemisphere lesions in areas known to induce both aphasia and apraxia more often induce aphasia. In one study only 20 of 35 aphasic patients were also apraxic (Heilman, 1975). The discrepancy between the incidence of aphasia and apraxia suggested that although in right-handers visuokinaesthetic (space-time) motor engrams for skilled movements are localized in the left hemisphere, the right hemisphere in many of these persons can substitute for the left. Because patients with large left hemisphere lesions in the region known to induce apraxia sometimes have aphasia without apraxia, it should not be surprising that callosal damage can induce not only verbal-motor disconnection apraxia but also ideomotor apraxia. Alternatively, the difference between our patient and the one described by Geschwind and Kaplan (1962) may not relate to brain organization but rather to the size of the lesion and its location.

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LIPIDS OF DEVELOPING BRAIN OF TWITCHER MOUSE

AN AUTHENTIC MURINE MODEL OF HUMAN KRABBE DISEASE

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SUMMARY

Brains of the newly discovered neurological mutant of the mouse, twitcher, were analysed from birth to the terminal stage of the disease for major tissue constituents and the lipid composition. A genetic deficiency of galactosylceramidase is the underlying cause of this mutant. The affected mice failed to gain body weight after 20 days (30 per cent of normal at 42 days) but the brain weight was much less affected (85 per cent of normal at 42 days). The water content and the four major fractions, chloroform-methanol insoluble residue, chloroform-methanol soluble protein, upper phase solids and total lipid, were essentially unaltered except that the total lipid was reduced slightly towards the terminal stage. Among lipids, only galactolipids, galactosylceramide and sulphatide were abnormal in the twitcher brain. Galactosylceramide was decreased at 37 and 42 days whereas decrease in sulphatide occurred earlier from 25 days, resulting in an increased ratio of galactosylceramide to sulphatide. The analytical abnormalities found in the twitcher brain are qualitatively similar to and quantitatively milder than those in the brain of human patients with globoid cell leukodystrophy (Krabbe disease), of which the twitcher is an enzymatically authentic animal model. The secondary abnormalities observed in brains of human patients as the result of tissue devastation were generally not present in the twitcher brain. Mouse brains contain relatively little myelin. As the pathology in twitcher is greatest in the spinal cord and brainstem (Duchen *et al.*, 1980), the fact that the changes in twitcher brains are quantitatively milder than those of human patients may partly reflect the relative amount of myelin in the two species. While more detailed studies of some specific constituents, such as galactosylsphingosine, and of other tissues, such as the peripheral nervous system and the kidney, will have to be performed, the present results serve as the reference for comparison between the human and murine galactosylceramidase deficiency states and for future experiments with the twitcher mutant, which is an invaluable tool for studies of globoid cell leukodystrophy.

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INTRODUCTION

Globoid cell leucodystrophy (GLD, Krabbe disease) in man is a rare genetic disorder caused by a deficiency of galactosylceramidase (EC 3.2.1.46) activity (Suzuki and Suzuki, 1970). Studies of human patients are severely restricted because of its rarity and for ethical reasons. Appropriate animal models can provide invaluable experimental tools for studies of pathobiology of the disease. Genetic GLD has been reported in three other relatively large mammalian species; cat (Johnson, 1970), sheep (Pritchard *et al.*, 1980), and dog (Fankhauser *et al.*, 1963; Fletcher *et al.*, 1966). Of these, no enzymatic confirmation was available for the feline disease. The sheep model did show profound deficiency of galactosylceramidase but, to our knowledge, no sheep colony with the disease has been established. The canine form of GLD occurs in pure breeds of West Highland and Cairn terriers as the result of genetic galactosylceramidase deficiency (Suzuki *et al.*, 1970). Since a colony of these dogs was maintained for research purposes, the canine model was used extensively for studies of genetic galactosylceramidase deficiency (*see* Suzuki and Suzuki, 1983, for review). However, the dog colony has recently been terminated (T. F. Fletcher, personal communication) and is therefore no longer available for research except for sporadic cases.

While the canine model alleviated some of the constraints associated with studies on human patients, its size, the limited number of litters, slow reproduction and the requirements for elaborate and expensive facilities for maintenance made it unsuitable for experiments that would require a large number of affected and/or heterozygous animals. The recently recognized murine mutant, twitcher, can overcome these disadvantages of the previously available animal models. The pathological alterations of the nervous system of affected mice are very similar to those of human patients (Duchen *et al.*, 1980) and the underlying genetic cause is also the deficiency of galactosylceramidase activity (Kobayashi *et al.*, 1980). On the other hand, even if caused by the same enzymatic defect, species differences are expected in the clinicopathological consequences and, therefore, detailed basic characterization is the prerequisite initial phase of the study in order to assure proper interpretation of the results of subsequent experiments. The present report describes in some detail the developmental changes in the lipid composition of twitcher brains.

MATERIALS AND METHODS

Animals

A colony of twitcher mice is maintained in the animal facility of this institution. The genetic status of each animal—affected, heterozygous and normal—is routinely determined within 10 days after birth by assaying clipped tails for galactosylceramidase activity (Kobayashi *et al.*, 1982). All animals were kept with their mothers and were weighed when they were killed. After 30 days, the standard laboratory animal chow was soaked in tap water and placed on the floor of the cage to facilitate feeding of affected mice. Artificial forced feeding was not employed. Under these conditions, it was difficult to maintain affected mice beyond 45 days. At least 1 normal, 2 affected and 2 heterozygous animals were killed at each time point, selected at intervals from 1 day to 42 days. Mice were killed by decapitation. Blood was blotted with filter paper, the brain carefully removed free of cranial nerves, and stored frozen in an air-tight container until analysed. All structures above the foramen magnum, including the cerebellum, were included in the specimen.

Analytical Procedures

Analyses were carried out within three months of storage. Five and 3 brains were pooled for each sample for 1-day and 8-day-old mice, respectively. Individual brains were analysed separately for all other ages. Brains from affected, heterozygous and normal mice of the same age were processed simultaneously. Wet weight of the brain was measured in a preweighed Potter-Elvehjem glass homogenizer tube. The brain was then extracted with 19 vol. of chloroform-methanol (2:1, v/v) with 70 strokes of a motor-driven glass pestle.

The general principle of lipid analysis was essentially as described previously (Suzuki *et al.*, 1969), based on the method of Folch *et al.* (1957). The 'chloroform-methanol insoluble residue', 'upper phase solids', 'chloroform-methanol soluble protein', and 'total lipid' fractions were weighed after complete desiccation. The sum of these four major fractions was the dry weight of the tissue.

The 'upper phase solids' fraction was dissolved in water and dialysed against water for 40 h at 4° C with at least 3 changes of water. After total ganglioside in the dialysed upper phase was estimated by determination of the sialic acid content (Svennerholm, 1957; Miettinen and Takki-Luukkainen, 1959), it was dried and dissolved in chloroform-methanol (1:1, v/v) to a sialic acid concentration of 0.5 $\mu g/\mu l$. Ten μl of this solution was applied as a 7 mm streak on a Merck high-performance silica gel 60 thin-layer plate (EM Laboratories, Englewood Cliffs, NJ). The plate was developed in chloroform-methanol-water (55:45:10, v/v/v) containing 0.02 per cent $CaCl_2 \cdot 2H_2O$, and ganglioside visualized by spraying the resorcinol reagent and heating (Ando *et al.*, 1978). Quantitative determination of individual gangliosides was done with Shimadzu CS-910 TLC scanner at 580 nm in the linear scanning mode, and the peak areas were calculated with Shimadzu CR-1A integrator-recorder. The ganglioside nomenclature was based on the system of Svennerholm (1963).

The total lipid fraction was dissolved in a known volume of chloroform-methanol (2:1, v/v) For a general semiquantitative view of individual lipids, 100 μg of the total lipid was chromatographed on the Merck high-performance silica gel 60 thin-layer plate in a solvent system of chloroform-methanol-water (70:30·4, v/v/v) and the spots were visualized by 50 per cent sulphuric acid spray and heating. Total cholesterol (Searcy and Bergquist, 1960) and total lipid phosphorus (Marinetti *et al.*, 1959; Norton and Autilio, 1966) were determined. Total phospholipid was estimated with an assumption that the average molecular weight of brain phospholipids is 775. Major phospholipids were separated by unidimensional thin-layer chromatography on silica gel G plates (Analtech, Newark, DE) in chloroform-methanol-concentrated ammonium hydroxide (65:25·5, v/v/v) and were visualized in iodine vapour. Each spot was scraped and the phophorus content determined directly (Norton and Autilio, 1966). The molecular weights used to calculate amounts of individual phospholipids were as described previously (Suzuki *et al.*, 1969).

Quantitation of galactosylceramide and sulphatide was by high-performance liquid chromatography (Nonaka and Kishimoto, 1979) except for a minor modification in the desulphation procedure. Benzoylated product, after drying, was dissolved in 0.25 ml of 7 per cent trifluoroacetic acid in ethylacetate and heated at 60° C for 45 min. The reaction mixture was evaporated to dryness and purified by partition in acetonitrile-hexane-water. Details of this modified procedure for sulphatide determination will be reported elsewhere (K. Shimomura and Y. Kishimoto, personal communication).

RESULTS

Determination of the genetic status of individual mice was unequivocal on the basis of galactosylceramidase activity in clipped tail (Table 1). These results were consistently confirmed by either galactosylceramidase activity in the spinal cord or kidney at the time of sacrifice or by the clinical disease for those mice killed at twenty-five days or thereafter. Evaluation of the results clearly indicated that there is no difference in the body weight, brain weight and in any other analytical parameters determined in this study between the genetically normal and heterozygous mice. Therefore, the data from these two groups are pooled into a single 'control' group hereafter, unless otherwise specified. The number of control samples at each time point was 4 (20 brains) at 1 day, 4 (12 brains) at 8 days, 5 at 15 days and 4 for all other ages.

TABLE 1 GALACTOSYLCERAMIDASE ACTIVITY IN CLIPPED TAILS OF MICE USED FOR BRAIN LIPID ANALYSIS

	Enzyme activity
Genetic status	*(nmol/h/mg protein ± SD)*
Normal	2.49 ± 0.45 (n = 28)
Heterozygote	1.30 ± 0.16 (n = 29)
Affected	0.29 ± 0.13 (n = 28)

Affected mice gained body weight normally until 21 days, after which time, however, they not only failed to gain weight further, but lost some weight towards the terminal stage (fig. 1). At 42 days the twitchers weighed less than 30 per cent of the control mice. Brain weight was much less affected than body weight. It tended to be slightly lower than controls at 33 days and was significantly lower at 37 days ($P < 0.004$) and 42 days ($P < 0.003$) (fig. 1). Even at the terminal stage, wet weight of the twitcher brain was 85 per cent of the control brain. While the proportion of the dry weight, relative to wet weight, increased during development, as expected, there were no statistically significant differences between the twitchers and the controls throughout the experimental period (fig. 1). This means that the dry weight per brain in the twitcher mice at the terminal stage is lower than the controls by the same percentage as the reduction in the wet weight. The developmental changes of the four major fractions in the twitcher brains generally followed the patterns of the control brains, on the basis of percentage of dry weight, except that there were small decreases in the total lipid at 37 days ($P < 0.11$) and 42 days ($P < 0.03$) (fig. 2).

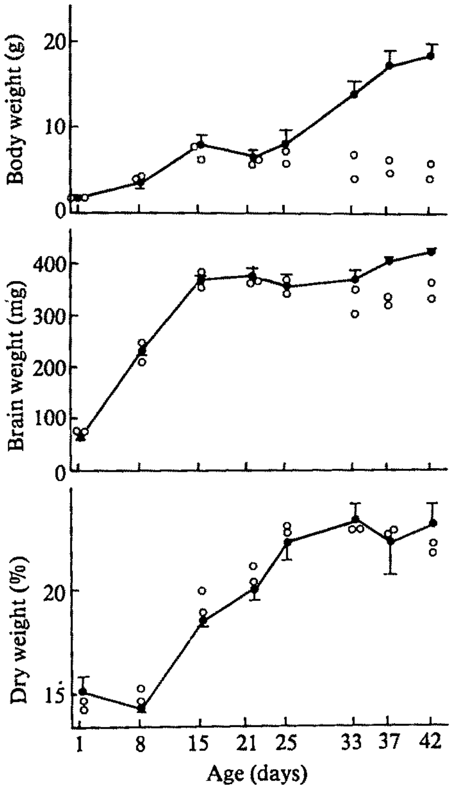

FIG. 1 The body weight, brain weight and dry weight of the brain of the twitcher mouse during development. The control values are given in closed circles with the standard deviations, while the values of the twitchers are given individually with open circles.

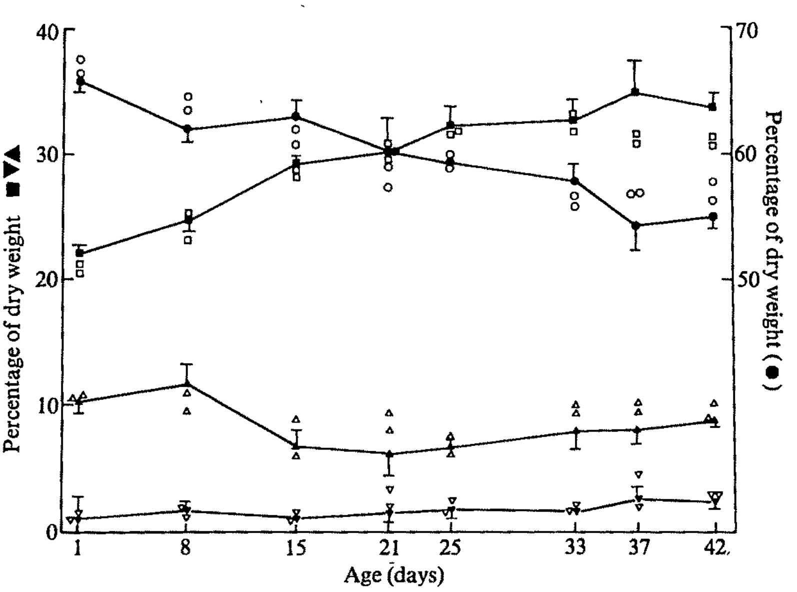

FIG. 2. The major constituents of the brain of the twitcher mouse during development. The control values are given in closed symbols with standard deviations, while the values of the twitchers are given individually with open symbols. Chloroform-methanol insoluble residue (● ○). Total lipid (■ □). Upper phase solids (▲ △). Chloroform-methanol soluble protein (△ ▲)

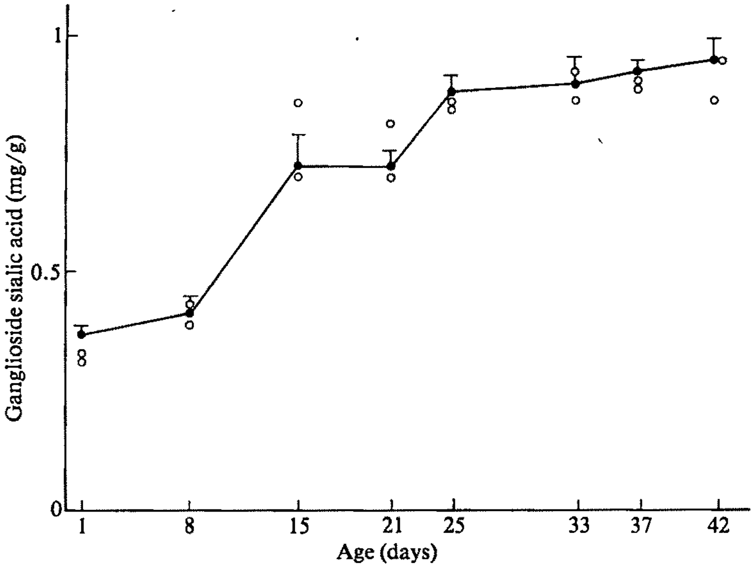

FIG 3. The total sialic acid in the ganglioside fraction of the brain of the twitcher mouse during development. The control values are given in closed circles with standard deviations, while the values of the twitchers are given individually with open cicles.

The total sialic acid in the dialysed upper phase increased during development on the basis of unit brain weight (fig. 3). Since the increment in the wet weight of the brain was greatest around 10 days, the increase in total ganglioside sialic acid per brain was also steepest at this period. No significant differences were found, however, between the affected and control mice. Proportions of individual gangliosides likewise showed developmental changes but no differences between the twitchers and the controls (fig. 4). The four major gangliosides, G_{M1}, G_{D1a}, G_{D1b} and G_{T1b}, and three minor gangliosides, G_{D2}, G_{D3} and G_{Q1b}, were quantitated separately throughout the development. Two minor spots with chromatographic mobility between G_{D1b} and G_{T1b} increased five-fold in proportion during development (G_{x1} and G_{x2}). Both were labile to mild alkaline treatment. Their exact structures were not determined.

Visual examination of thin-layer chromatograms of the total lipid fractions indicated that there were no discernible differences between the twitchers and the controls up to 33 days. At 37 days, the proportion of galactosylceramide appeared possibly lower and at 42 days clearly lower than the controls. The quantitative determinations essentially confirmed the visual impression (*see below*). The total cholesterol, total phospholipids and the individual major phospholipids in the twitcher brains followed the normal developmental changes (fig. 5).

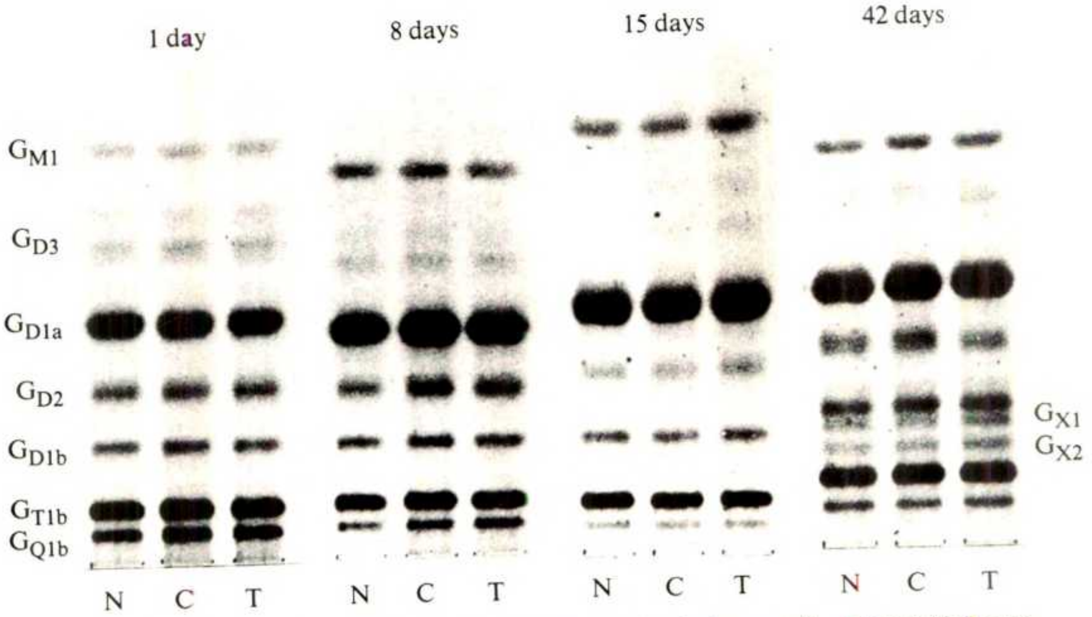

FIG. 4. Thin-layer chromatography of mouse brain gangliosides during development. The technical details were as described in the text. N = normal. C = carrier. T = twitcher. Since this figure is a composite of four thin-layer chromatograms, migrations of individual gangliosides are not necessarily identical.

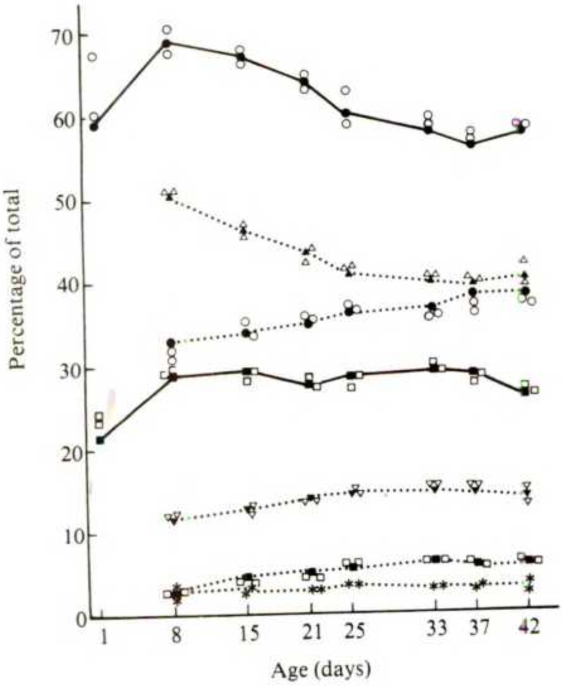

FIG. 5. Cholesterol and phospholipids in the brain of the twitcher mouse during development. The values for controls are in closed symbols and those for twitchers are in open symbols. Total phospholipids (●—○). Total cholesterol (■—□). Phosphatidylcholine (▲ - - - △). Ethanolamine phospholipids (● - - - - ○). Serine phospholipids (▼ - - - ▽). Sphingomyelin (■ - - - - □). Phosphatidylinositol (* - - - - *). (Only the values for the twitchers are given but the control values were identical with the twitcher values.) Total cholesterol and total phospholipids are expressed as a percentage of total lipid, while the individual phospholipids are given as a percentage of total phospholipid. In order to avoid cluttering the graphs, standard deviations for the controls are omitted. They were always within ± 5 per cent or less of the means.

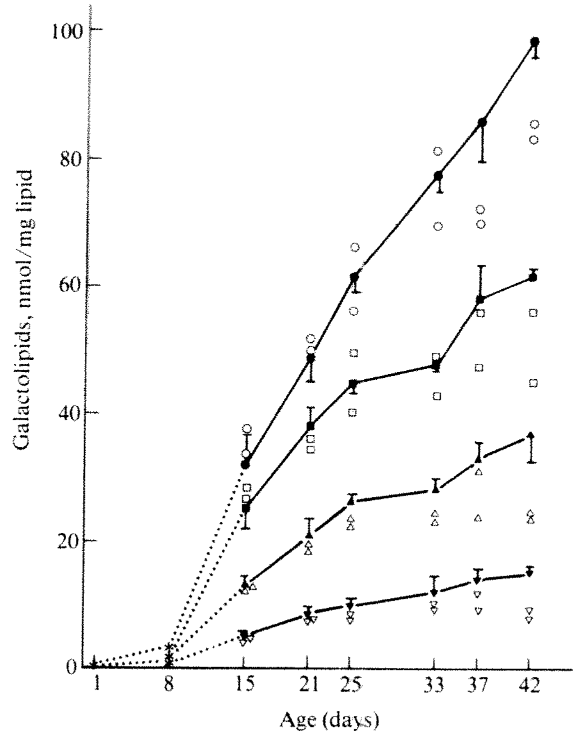

FIG. 6. Galactosylceramides and sulphatides in the brain of the twitcher mouse during development. The control means are given in closed symbols with standard deviations while the values for twitchers are given individually in open symbols. The values for 1 day and 8 days were too low for the scale of this graph and they are given in Table 2. The dotted lines indicate approximations for these time points. HFA-gal-cer (● ○). NFA-gal-cer (■ □). NFA-sulphatide (▲ △). HFA-sulphatide (▼ ▽).

Both galactosylceramide and sulphatide increased drastically after 8 days, concomitant with the period of active myelination in both the control and the twitcher mice (fig. 6, Table 2). At 1 day, α-hydroxy fatty acid-containing galactosylceramide (HFA-gal-cer) in the twitcher brain appeared higher than normal, while nonhydroxy fatty acid-containing galactosylceramide (NFA-gel-cer) and both types of sulphatides (HFA-sulphatide and NFA-sulphatide) were normal (Table 2). Since the amounts were extremely small at 1 day and thus the signal-to-noise ratio poor, this apparent difference should be interpreted with caution. Both

TABLE 2. BRAIN GALACTOLIPIDS IN EARLY DEVELOPMENT

	1-day old		*8-day old*	
	Control ($n = 4$)	*Twitcher* ($n = 2$)	*Control* ($n = 4$)	*Twitcher* ($n = 2$)
*Galactolipid**	(*nmol/mg lipid*)			
NFA-gal-cer	0.046 ± 0.020	0.06, trace	1.40 ± 0.40	1.78, 1.16
HFA-gal-cer	0.370 ± 0.060	0.80, 1.06	3.34 ± 0.56	5.00, 3.88
NFA-sulphatide	0.62 ± 0.26	0.60, 0.42	2.48 ± 0.58	2.72, 2.14
HFA-sulphatide	0.26 ± 0.08	0.30, 0.38	1.02 ± 0.34	1.20, 0.82

* NFA = nonhydroxy fatty acid. HFA = α-hydroxy fatty acid. The control values are given as the means ± SD, while individual values are given for the twitcher samples. Five brains were pooled for a sample at 1 day and three brains for a sample at 8 days.

HFA- and NFA-gal-cer, however, were normal in the twitcher brain from 8 to 33 days. At 37 and 42 days, HFA-gel-cer in twitchers was significantly lower than the controls ($P < 0.05$ at 37 days and $P < 0.002$ at 42 days). NFA-gal-cer was significantly lower only at 42 days ($P < 0.02$). On the other hand, both types of sulphatides, particularly HFA-sulphatide, were decreased earlier than galactosylceramides; at 25 days ($P < 0.02$ for NFA-sulphatide and $P < 0.005$ for HFA-sulphatide), at 33 days ($P < 0.003$ for NFA-sulphatide and $P < 0.002$ for HFA-sulphatide) and at 42 days ($P < 0.03$ for NFA-sulphatide and $P < 0.005$ for HFA-sulphatide).

DISCUSSION

In human globoid cell leucodystrophy (GLD) it is practically impossible to examine the evolution of the disease process from the early stages because available specimens are inevitably from the terminal stage. Even in the canine form of the disease, it is difficult to obtain a large number of specimens. Thus there has been no study in man or in animal models with GLD concerning the changes of the lipid composition of the brain throughout development. On the other hand, there are many analytical studies of brain lipids in human patients at the terminal stage available in the literature (*see* Suzuki and Suzuki, 1983, for review), the most extensive series being that by Vanier and Svennerholm (1974*a*, *b*, 1975). The twitcher mouse offers a unique opportunity to follow the biochemical evolution of the disease process and also to compare the findings at the terminal stage with those of the human disease. Identification of the genetic status immediately after birth on clipped tails permits reliable sampling well in advance of the clinical onset of the disease.

The major and perhaps the most surprising finding in the present series of the survey analysis of brain lipids in twitcher mice is that the composition of the brain lipids remains remarkably close to normal even at the advanced stage of the disease. A dramatic decrease in the total lipid and an increase in water content occur in the brain of human patients, more severely in the white matter but also in the gray matter (*see* Eto and Suzuki, 1971; Vanier and Svennerholm, 1974*a*). Only a slight decrease in total lipid and practically no change in the water content were observed in the twitcher even at the terminal stage. The associated reduction in cholesterol, the relative decrease in ethanolamine phospholipids and the relative increase in phosphatidylcholine found consistently in human patients were not apparent. Only the galactolipids, galactosylceramide and sulphatide were significantly decreased in the twitcher brains in later stages of the disease but the degree of the decrease was much milder than that in human patients. For example, the data of Vanier and Svennerholm (1974*a*) on 19 cases of human patients, ages 7 to 32 months, showed galactosylceramide levels from 40 per cent of normal in the youngest specimen to well below 10 per cent in others. In contrast, galactosylceramide in the 42-day twitcher brain was 80 to 85 per cent of the controls and sulphatide 60 to 65 per cent of the controls on the basis of wet weight of the brain. Similarly, there were essentially no alterations in the total amount or in the proportions of ganglioside in the twitcher brain at any stage in contrast to the finding of Vanier and Svennerholm (1975). In human patient brains they found reductions of G_{D1a} and G_{M1} and relative increases of G_{D2} and G_{D3}.

These findings are consistent with the pathological findings of twitcher brain. Although clinical manifestations become apparent around 20 to 23 days, myelination in the early stages is essentially normal with thinning of the myelin sheath around the axons of larger diameter detectable at 20 and 30 days only by extensive morphometric analysis (Nagara *et al.*, 1982). Globoid cell infiltration is also moderate up to this stage, although these cells appear in small numbers from very early stages. In human GLD it is generally accepted that myelination is never normal and 'numerous' globoid cells have been observed in the spinal cord of an affected fetus aborted at 22-week gestation (Ellis *et al.*, 1973). Human patients are cared for much more intensively and thus survive to later stages than mice. Much more extensive alterations are expected in brains of human patients. Nevertheless, human GLD appears to affect the CNS much more severely from early stages of the disease. The species differences, such as this, make it imperative to characterize the twitcher mutant in detail pathologically and biochemically before experimental results can be interpreted with confidence.

Since the fundamental genetic defect is in galactosylceramidase activity and since the most profound abnormalities in the brain of human patients occur in galactolipids, special attention must be focused on the galactolipids. One of the most unusual features of human GLD is the lack of abnormal accumulation of galactosylceramide despite the block in the catabolic pathway. Although the level was not as low as those seen in human cases, galactosylceramide also does not accumulate abnormally in the twitcher brain. The most consistent finding in human GLD is the increase in the galactosylceramide to sulphatide ratio (Vanier and Svennerholm, 1974*a*; Suzuki and Suzuki, 1983). It is interpreted to mean that the low sulphatide level is more representative of the myelin loss, while the relative preservation of galactosylceramide is indicative of its presence within the globoid cells as a undegraded material due to the genetic defect. The same phenomenon occurs in the twitcher, most likely for the same reason. The sulphatide level was significantly lower than that in the controls already at 25 and 33 days when the galactosylceramide level was still normal.

In the present series of studies designed for a broad analysis of brain lipids, it was not possible to examine other minor glycolipids. The white matter of human patients contains abnormal amounts of more complex glycoplipids, lactosylceramide, galactosyl-galactosyl-glucosylceramide, globoside and the blood group substance H (Eto and Suzuki, 1971; Vanier and Svennerholm, 1975; Svennerholm *et al.*, 1980). They are interpreted as being localized in the globoid cells which are of mesodermal origin. Analysis of these glycolipids requires much larger samples than a single mouse brain and therefore pooling of several brains. Another important galactolipid related to the pathogenesis of GLD is galactosylsphingosine (psychosine). It is also a natural substrate of galactosylceramidase (Miyatake and Suzuki, 1972*a*, 1974) and thus cannot be degraded in GLD (Miyatake and Suzuki, 1972*b*). The 'psychosine hypothesis' was developed as the biochemical pathogenetic mechanism of GLD based on the highly cytotoxic nature of galactosylsphingosine (Suzuki and Suzuki, 1983). In the human disease, strong support for the hypothesis was provided by Svennerholm *et al.* (1980) who showed at least 10- to 100-fold increases of galactosylsphingosine in the white matter of five patients over the essentially unmeasureable normal level. The possibility of its presence in twitcher brains would be of interest. The analytical technique of Svennerholm *et al.* (1980) requires more than 5 g of white matter. A more sensitive method therefore must be developed before galactosylsphingosine analysis can be attempted on twitcher brains.

Attention should also be directed to tissues other than the CNS. In the human disease, the PNS is moderately but consistently involved, with segmental demyelination manifested by reduced conduction velocity (Suzuki and Suzuki, 1983). From the available information, the PNS in the twitcher mice is affected earlier and more severely than the CNS, suggesting another important point of species differences (Duchen *et al.*, 1980; Kinuko Suzuki, personal communication). In the kidney of human patients, there is no accumulation of galactosylceramide despite the normal histology and function and the catabolic block (Suzuki, 1971). This finding prompted a speculation for a regulatory reduction of galactosylceramide synthesis as a possible explanation for the lack of abnormal accumulation. Our recent metabolic study appeared to exclude this possibility (Kodama *et al.*, 1982) but the level of galactosylceramide in the twitcher kidney needs to be ascertained for a more conclusive interpretation.

The analytical studies discussed above which all require larger amounts of tissues or more sensitive methods than the initial survey analysis presented in this report are planned for the near future.

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CRITICAL PERFUSION OF BRAIN AND RETINA

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SUMMARY

Four patients with extensive occlusive disease of the extracranial arteries are described. All suffered attacks of visual loss due to transient retinal ischaemia and all developed the haemorrhagic changes of low-flow retinopathy. Resting cerebral blood flow was within normal limits in all patients. The attacks were provoked by falls in systemic blood pressure or, in one patient, by facial heating. The probable mechanism in this last case is thought to be diversion of blood to a dilated external carotid vascular bed. Temporary cerebral and brachial symptoms occurred but no permanent changes developed. Successful surgical reconstruction was achieved in two patients with relief of symptoms.

INTRODUCTION

The term 'haemodynamic crisis' was introduced by Denny-Brown (1960) to denote a temporary reduction in blood flow to a focal area of brain resulting in a transient ischaemic attack. He proposed that a short-lived fall in blood pressure was the usual cause of such an attack and that regional ischaemia occurred because the circulation to a part of the brain was already compromised by local vascular disease.

The fact that many patients with transient ischaemia were found to have normal blood pressures during attacks and the rarity with which artificially induced hypotension gave rise to focal symptoms led many to discard haemodynamic crisis as a cause of transient cerebral ischaemia in favour of embolism from the heart or large arteries (Kendell and Marshall, 1963; Gunning *et al.*, 1964).

Patients with multiple extracranial arterial occlusion are an unusual group who may present with temporary attacks of visual or cerebral disturbance before developing permanent structural change in the eye and brain. Four such patients are described. The factors which provoked attacks included systemic arterial hypotension, venous hypertension and extracerebral steal. These observations support Denny-Brown's concept of a critical perfusion state and suggest that the retina may be a more sensitive indicator of insufficiency than the brain.

CASE REPORTS

Case 1

L.R., a 53-year-old engineer, complained in 1980 of episodic visual disturbances in the left eye for the previous four months. He had a long history of vascular disease. In 1972, after eight years of intermittent claudication of the right calf and buttock, he underwent right iliac endarterectomy. He was then well until 1975 when, following development of similar symptoms in the left leg, he was found to have stenosis and atheroma of the distal aorta and both common iliac arteries. An aortofemoral graft relieved his symptoms. At about this time he developed mild angina pectoris and a left carotid bruit was noted. In July 1980 he had a sudden partial loss of vision in the left eye which lasted about five hours. The whole visual field became blurred and abnormally bright; he recovered completely. At the same time as the visual symptoms he had pain in the left side of the neck and head, mild difficulty with word finding and weakness and numbness of right hand. He found himself quite unable to write. Weakness recovered over the next few days. He continued to have attacks of visual loss in the left eye, occurring two or three times a week, lasting up to two hours, sometimes with difficulty in reading and writing but with no speech disturbance.

Examination at this time showed he was fully alert and had no abnormal neurological signs. In the cardiovascular system the pulse was regular at 68/min, blood pressure was 160/80 in the right arm and 110/90 in the left. A pulse could be felt on both sides of the neck; that on the right was stronger and there were bilateral bruits. Carotid angiography *via* a femoral catheter showed severe stenosis of the right internal carotid artery; the catheter could not be introduced into the origin of the left common carotid artery. Endarterectomy of the origin of the right internal carotid was performed using a Javid shunt. He made a good postoperative recovery and was free of all symptoms for a time.

He returned to the clinic six months later complaining of continuing visual disturbance affecting the left eye occurring several times a day. The main precipitating factor was heat, particularly on his face or head. Sunlight had the same effect and initially he was not sure whether heat or glare was responsible. He found that entering a hot room, having a hot bath or climbing stairs would regularly provoke an attack. The attacks consisted of a bright dazzling sensation coming on over about a minute. Acuity was not significantly affected but contrast was. Bright objects appeared lighter whereas dark objects became difficult to see. The edges of bright objects appear to flicker and the overall effect was one of 'over-exposure'. When he read typed words during an attack the paper became patchy and appeared like 'a very poor photocopy'. Sometimes the attacks were accompanied by a dull pain above the left eye but there was no diplopia, faintness or other symptoms. His vision returned to normal quickly after the stimulus was removed. He had no symptoms suggestive of cerebral ischaemia. It was possible to provoke these attacks regularly by playing a hair drier on his face or head for a few minutes or by asking him to perform vigorous exercise such as climbing stairs.

Examination at this time showed some significant changes. The right carotid artery remained palpable and with a systolic bruit; the left carotid artery was impalpable and silent. Arch angiography confirmed complete left common carotid occlusion with slight residual stenosis on the right (fig. 1). Visual acuity was 6/6, N5 on the right and 6/5-3, N5 on the left. Pupil reactions and eye movements were normal, as were the visual fields. Examination of the fundus on the right was normal but on the left there were the features of low-pressure retinopathy with dilated retinal veins, peripheral microaneurysms and blot haemorrhages; the arteries at the disc pulsated with the lightest digital pressure on the globe. Fluorescein angiography showed very slow arterial flow with peripheral closure and some macular oedema (fig. 2A–C).

The left carotid system was explored surgically (Professor N. L. Browse). Complete occlusion by atheroma and thrombosis was found at the origin of the left common carotid artery. On opening the artery there was no up-flow or back-flow. It had been hoped to anastomose the left subclavian to the

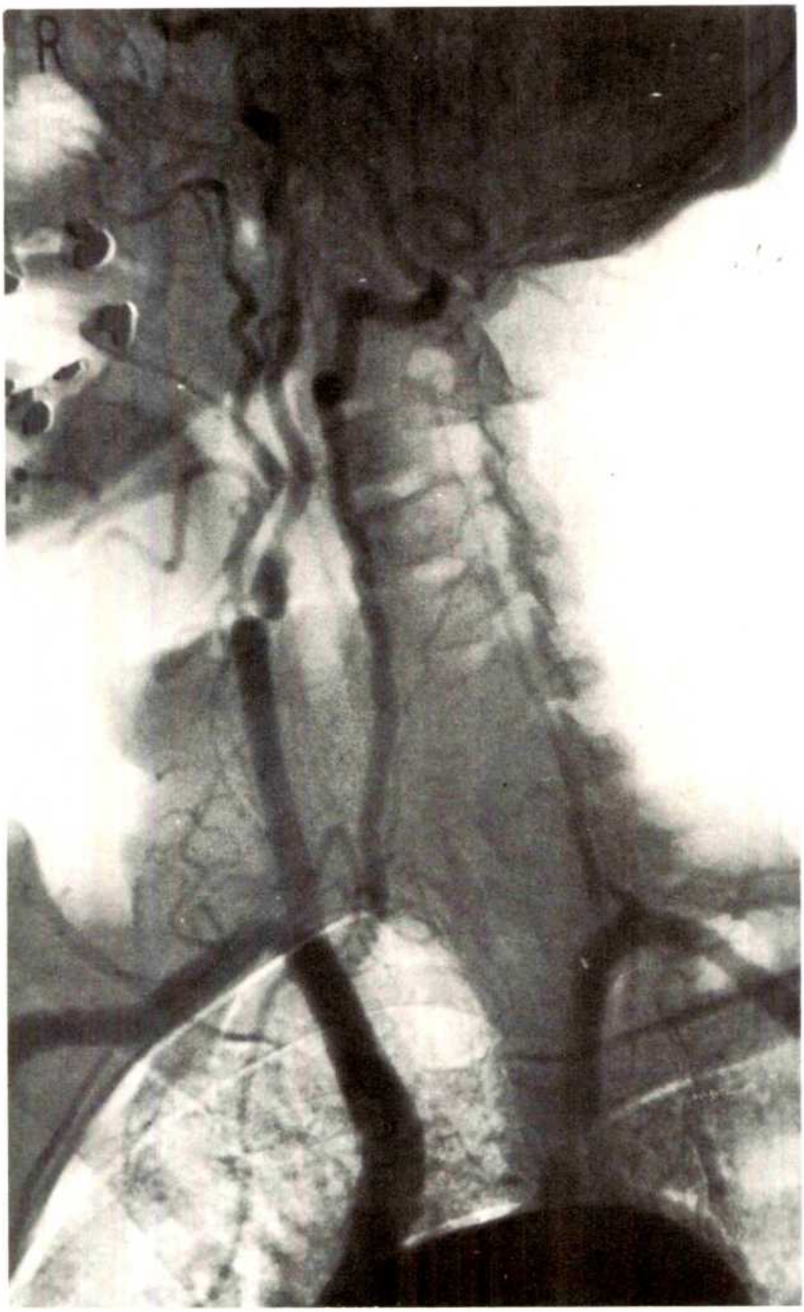


FIG. 1. *Case 1.* Arch angiography showing absence of filling of the left carotid system. The origin of the right nternal carotid shows some residual stenosis following endarterectomy. The left vertebral is small; filling is slow but interograde; the left subclavian shows mild stenosis.

left internal carotid artery but this proved impossible and after opening the artery the internal, external and common carotid arteries were ligated. Recovery was uneventful.

In the following six months the patient continued to have attacks of visual loss but with decreasing frequency.

Comment. This patient's unusual visual symptoms were of retinal origin. Investigations (Table 1), including retinal photostress test, showed no indication of delayed retinal metabolism. Ophthalmodynamometry showed a low resting retinal perfusion pressure and the further reduction during an attack suggests that the mechanism of an attack was diversion of blood to the dilated facial vascular bed causing temporary retinal oligaemia on the affected side.

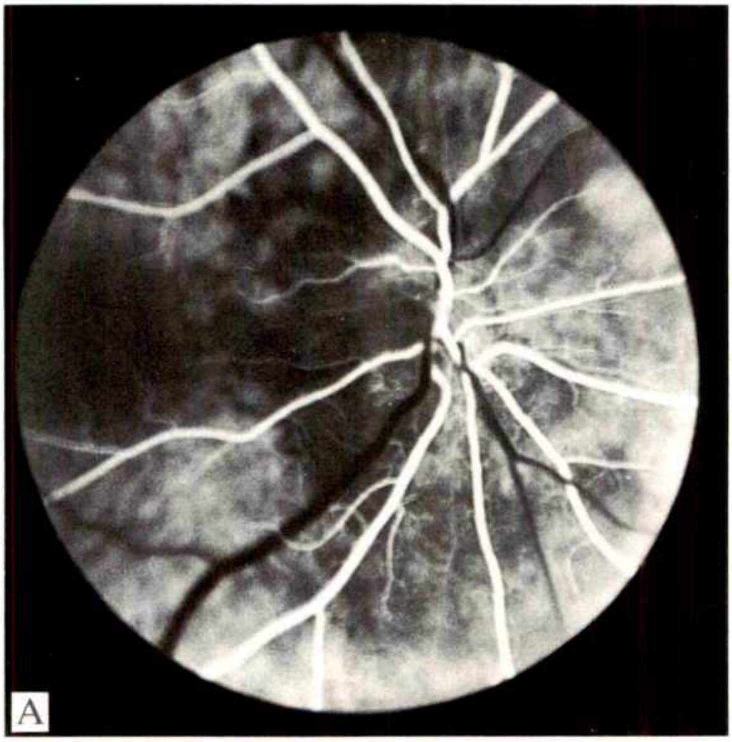
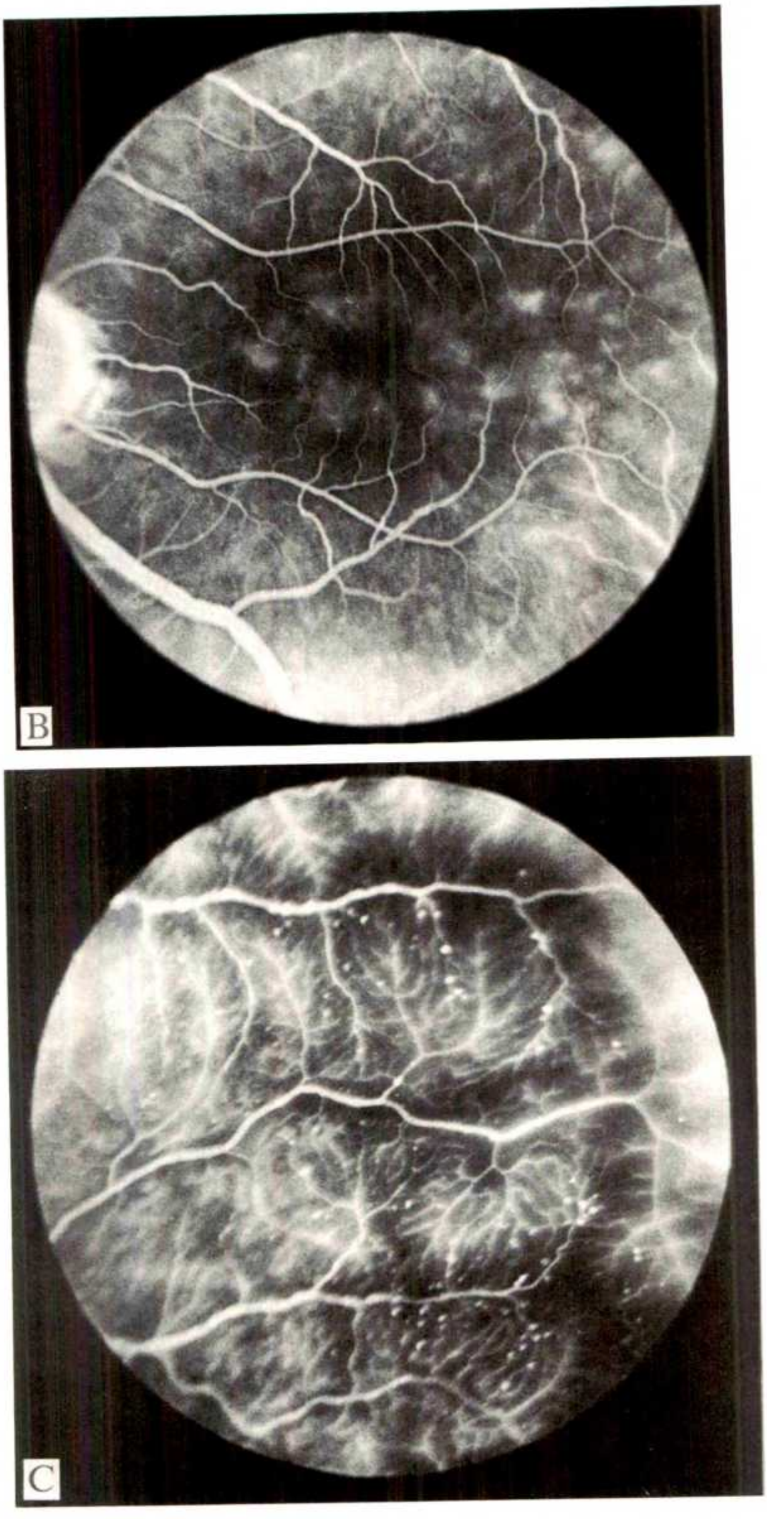


FIG. 2. *Case 1*. A, fluorescein angiography of the left retina showing marked retardation of blood flow. At this stage of arterial filling, dye would normally be visible in veins draining the posterior pole. B, later phase showing leakage of dye around the macula. C, peripheral retina showing irregularity of calibre in small veins and arteries with numerous capillary microaneurysms.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C

TABLE 1. SUMMARY OF INVESTIGATIONS IN CASE 1

	Right eye		*Left eye*		*Comment*
	Amplitude (μV)	*Latency (ms)* (*n 95–113 ms*)	*Amplitude* (μV)	*Latency (ms)*	
Visual evoked potential P100					
Standard pattern	7.2	108	4.5	110	Consistent interocular difference in amplitude–decrease in L eye
Small central pattern	5.0	107	3.2	110	
Large pattern	9.6	110	7.0	112	
Electro-oculogram	Light rise (n > 250%)	267%	245%		Marginal reduction on left
Electroretinogram b wave:a wave ratio			Scotopic (b:a normally = > 2.0:1)	b:a = 1.2:1	Suggests dysfunction of inner retinal layers
			Photopic (b:a normally = > 1.8:1)	b:a = 0.9:1	
Macular photostress times to recovery of visual acuity	2 min 30 s		2 min 40 s		No delay in pigment resynthesis
Ophthalmodynamometry	Resting (BP 150/110)	130/80	40/25		Mean of 6 measurements. Low perfusion pressure on left, further reduced on heating
	Heating face (BP 180/110)	120/65	32/17		

Case 2

M.S., a 37-year-old housewife, in December 1980 developed intermittent visual loss in the left eye. Attacks occurred on most days as she was rising from bed and lasted a minute or two. They increased in frequency up to about 20/day and were provoked by any minor exertion or sometimes by assuming an upright posture. A grey mist would pass across the left eye from the temporal to the nasal field and persist for about one minute. She could not see through the mist and it cleared in the same direction. On some occasions vision in that eye appeared fragmented during an attack. She had no other symptoms during the attacks and at other times her vision was perfectly normal. The episodes continued over the next six months and during this period she began to feel increasingly mentally and physically lethargic. Her appetite deteriorated and she lost about 8 kg in weight. A further factor in her weight loss was an aching pain in the jaw muscles after chewing.

In September 1981 she noticed pupillary inequality (left larger than right). At about this time she had some difficulty in reading so that after four or five lines she could not remember what she had read before. She had no other symptoms of impaired cerebration and no lightheadedness, loss of consciousness or symptoms in her arms.

On the day before admission she had toothache and felt a little faint. The following day she awoke with tunnel vision in the right eye and felt tired and was sweating. Later that day she tried to stand up and found she could not move properly, her limbs seemed heavy and would not respond; she felt mentally sluggish as though drugged. She was admitted to hospital.

In the past there had been no significant illness apart from an acute depressive episode one month before the onset of visual symptoms. There was a family history of atherosclerosis and her father had undergone carotid endarterectomy.

On examination she appeared anxious and was mildly confused. There was a tachycardia of 110/min and the blood pressure, which could not be taken in the arms, was 95/70 in the right leg. The skin and subcutaneous tissue of the head and neck were well nourished with no tenderness. There was no hair loss. There were weakly palpable right superficial temporal and right carotid pulses (the latter with a soft bruit), but all pulses were absent on the left. No pulse was felt in either arm but was normally present in the legs.

Neurological examination was normal. The right visual acuity was 6/18 and left 6/9. There was an incomplete Horner's syndrome on the right and also a right relative afferent pupillary defect. The visual field on the right was generally constricted. The right eye had a pale, swollen optic disc with superficial peripapillary haemorrhages. There were dilated veins and the central retinal artery collapsed at the lightest pressure touch on the globe. In the left eye the disc appeared slightly hyperaemic and the veins were dilated with some small peripheral microaneurysms visible. Ophthalmodynamometry showed reduced retinal artery pressure. These were therefore features of bilateral low-pressure retinopathy with an acute ischaemic optic neuropathy superimposed in the right eye. The ESR was 50 mm/1 h.

The diagnosis of aortic arch syndrome was confirmed by aortography (fig. 3). The innominate

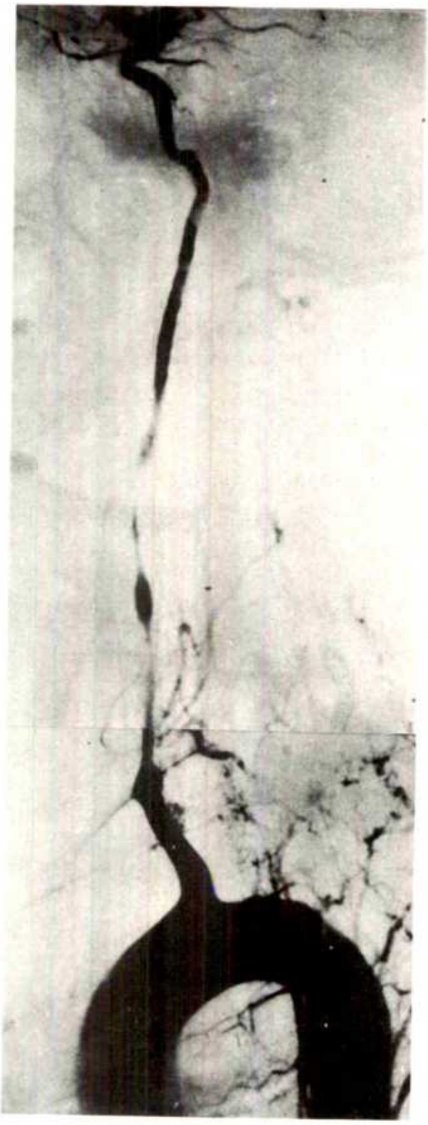

FIG. 3. *Case 2.* Arch angiography showing filling only of the innominate and right common carotid arteries. Both subclavian arteries and the left common carotid artery are occluded.

artery filled well but only the lowest portion of the right common carotid artery was normal. Above this the artery tapered and the external carotid artery did not fill. With selective catheterization an attenuated right internal carotid artery could be seen and there was a normal intracerebral circulation. The right subclavian artery did not fill and neither did the left subclavian nor left common carotid. The vertebral arteries showed late anterograde filling *via* muscular collaterals.

At operation (Professor N. L. Browse) a right aorta-internal carotid dacron graft was inserted with ligation of the common carotid and external carotid arteries. Postoperative progress was satisfactory although she developed widespread temporary deep retinal haemorrhages in the right eye. The retinal arterial pressure in the right eye was 50/35. On the left, visual acuity improved to 6/6 with subjective increase in clarity. The veins became less dilated and the central retinal artery pressure improved to 32/25. She has had no further attacks of amaurosis fugax in the left eye and the right vision has remained unaltered with tunnel field. The optic disc has become pale and the haemorrhages have resolved.

She is receiving long-term corticosteroid treatment (prednisone 10 mg/day). The ESR is 20 mm/h.

Histological examination of a portion of carotid artery showed fibrous thickening, destruction of elastic tissue and focal collections of lymphocytes compatible with arteritis. No marked features of atherosclerosis were seen.

Comment. This patient had extensive extracranial arterial disease of arteritic type with only one surviving carotid artery supplying the whole brain. The initial symptoms of retinal insufficiency in one eye were provoked by standing and by exercise. She also had ischaemic exercise pain in the jaw muscles on chewing. Symptoms of generalized cerebral ischaemia (faintness, fatigue, impaired concentration) were mild compared with the visual symptoms.

Case 3

H. H., a 26-year-old female Burmese student, was well until the age of 17 years when, following a non-specific febrile illness lasting for some months, she developed attacks of loss of vision in the left eye. Ophthalmoscopic examination at this time showed numerous retinal haemorrhages, venous dilatation and microaneurysms with some macular oedema. The retinal arteries were attenuated. A diagnosis of retinal venous thrombosis was made. Within a year a similar condition was noted in the right eye. Low intraocular tension and rubeosis of the iris gradually developed; her sight became permanently impaired by bilateral cataracts. Following cataract extraction there was a short-lived improvement of vision but a series of vitreous haemorrhages occurred in both eyes leading eventually to retinal detachment and permanent blindness within two years of the onset of symptoms.

At about the same time as the visual symptoms she began to suffer from attacks of loss of consciousness. At first these occurred about once a week but increased to two or three times daily. They occurred only when she was upright and were often provoked by standing or by minor exercise. She would fall to the ground without warning and remain unconscious for up to five minutes. She was sometimes incontinent and occasionally there were tonic movements of all limbs. On recovering consciousness she complained of general tiredness but was otherwise normal. No brachial pain or difficulty in chewing was noted. She had received a small dose of prednisone 5mg/day for three years.

On examination she was an intelligent oriental girl who was totally blind from extensive retinal detachment. The nervous system was intact. All pulses in the arm were absent but the fingers were warm and showed no features of ischaemia. A rapid postischaemic flush occurred after release of an arm cuff inflated to 150 mm Hg for two minutes. The right carotid pulse could just be felt but the left was absent as were both superficial temporal pulses. No cervical bruits were heard. Skin, hair and facial features were all normal. All the leg pulses were easily palpable, blood pressure was 130/80 in the leg. No abdominal bruit was heard.

Angiography (fig. 4A, B) showed almost complete occlusion of the brachiocephalic, left common carotid and left subclavian arteries at their origins from the aortic arch. The brain was perfused by

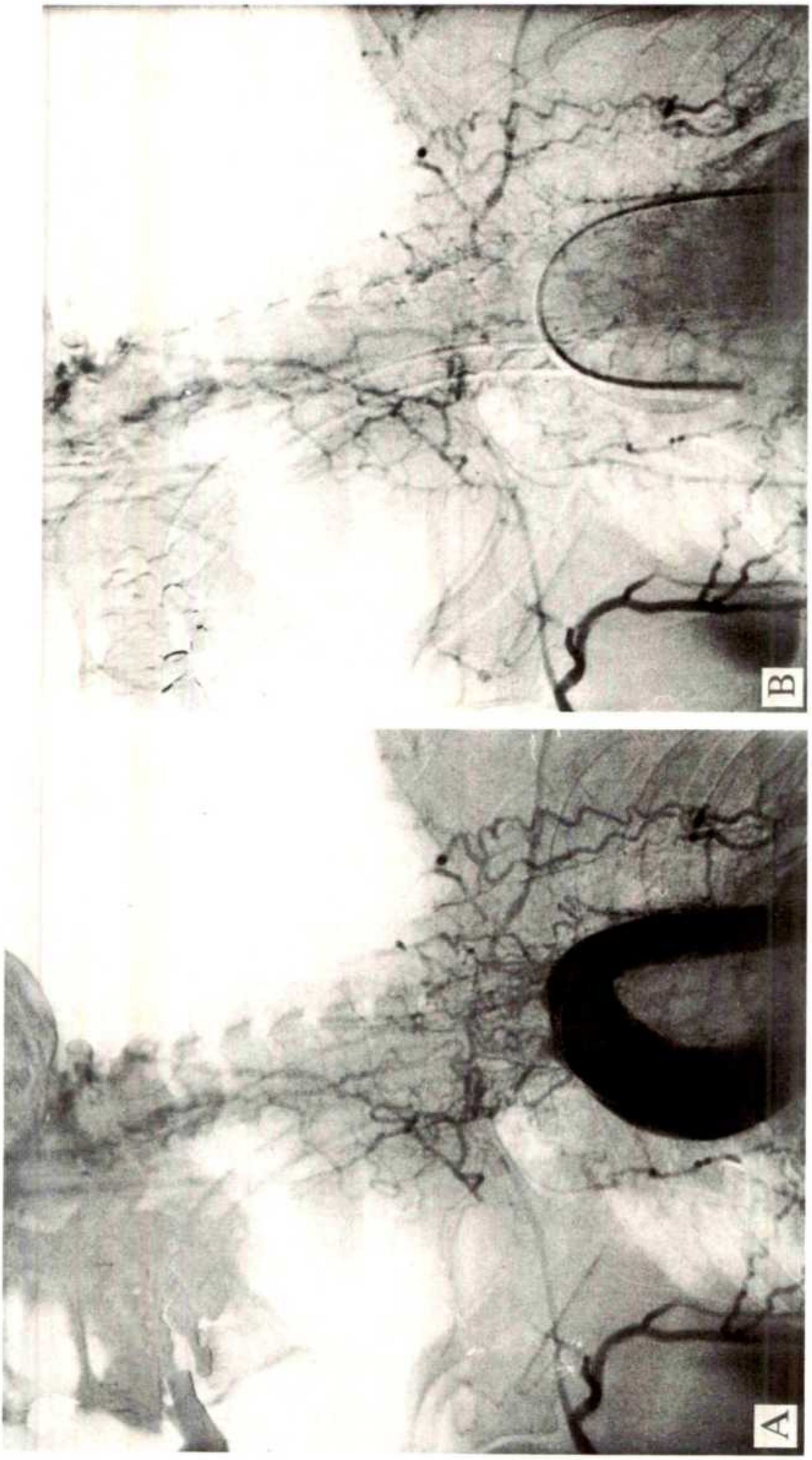

FIG. 4. *Case 3.* A, arch aortography showing almost complete occlusion of all major arteries arising from the aortic arch. B, later view showing filling of the carotid bifurcation and distal vertebral arteries on both sides *via* collateral arteries.

extensive collaterals derived from the vestiges of the great vessels and from the intercostal arteries which connected with muscular branches of the thyrocervical and costocervical trunks. Cerebral blood flow measured by the intravenous ^{133}Xenon technique was within normal limits; there was no regional variation (Table 2). A blood count was normal but the ESR was 33 mm/h.

A bilateral aortocarotid bypass was fashioned by Professor N. L. Browse by anastomosis of the stem of a Y-shaped dacron graft to the aorta. The two limbs were joined end to side to each internal carotid artery, which were found to be patent and showed moderately good back-flow when opened. Following operation recovery was rapid and uneventful. Superficial temporal pulses could be felt on both sides; no further syncopal attacks occurred on changes of position or on exercise. Her blindness was unchanged.

Histological examination of an arterial biopsy showed extensive fibrous thickening of the media and adventitia. Chronic inflammatory cells infiltrating the intima, but not the media or elastica, were seen.

Comment. This patient with arteritis extensively involving the aortic arch presented with intermittent visual loss which progressed to cataract and retinal detachment. At a later stage she developed temporary cerebral insufficiency with attacks of loss of consciousness related to standing and to exercise. All the major extracranial neck arteries were extensively involved.

TABLE 2. CEREBRAL BLOOD FLOW MEASUREMENTS. IV ^{133}XE TECHNIQUE (FAST FLOW)

	Mean hemisphere CBF (ml/100 g/min)	*$PaCO_2$ K Pa*
Case 1	Left 53.5	4.6
	Right 54.2	
	CO_2 reactivity 1.2 % (n 3–6)	34–42 mm
Case 2	Left 50.5	4.8
	Right 52.3	
Case 3	Left 61 (preop)	4.4
	Right 62	
	Left 85 (postop)	4.4
	Right 84	
Case 4	Left 51	4.2
	Right 52	

Case 4

E.M., a 65-year-old left-handed builder in April 1981 developed amaurosis fugax in the right eye. When seen a month later he had had 5 attacks, all of rapid onset and short duration with complete loss of vision described as 'a shutter passing across the eye'. He had 3 previous myocardial infarcts and also suffered from chronic obstructive airway disease. At this time retinal examination showed no abnormalities. There was a loud right carotid bruit; the carotid pulses and all peripheral pulses were normal. The heart rate was regular and blood pressure 150/80. In view of the history of cardiac disease he was not considered suitable for operation; on treatment with soluble aspirin the amaurosis fugax reduced in frequency and ceased after two months.

In October 1981, attacks of a different kind of visual disturbance began in the same eye. Sight gradually became patchy and fragmented and he described the appearance as 'a negative of a photograph'. He could discern shapes and colours but could not read with the right eye. The attacks lasted up to two hours and occurred about once a day. Shortly after this he developed episodic loss of use of the left arm and leg. On occasions when he used the left arm above his head, as when wiping a misted window, the left arm and leg lost all strength and jerky involuntary movements occurred lasting for about two minutes. Sometimes these coincided with visual loss. In one severe attack he fell to the ground with complete left-sided paralysis and at the same time was unable to speak for a few minutes.

Further examination showed the right superficial temporal artery pulse was now weak and delayed and the right common carotid pulse could not be felt, there was no bruit. The right fundus showed dilated veins and blot haemorrhages in the periphery. The central retinal artery collapsed on very light pressure on the globe. The left fundus was normal. There was no neurological deficit and no other change from the previous examination.

Ultrasound examination of the carotid bifurcation suggested common carotid artery occlusion on the right. There was also evidence of disease at the carotid bifurcation on the left by Doppler imaging which showed a tight stenosis of the external carotid artery. No epileptic discharges were seen on the electroencephalogram and a CT brain scan was normal. Fluorescein angiography showed delayed flow in the right retinal artery circulation. Ophthalmic artery systolic pressure was 50 mm Hg lower on the right as compared with the left. Cerebral blood flow measured by intravenous ^{133}Xenon technique was normal (Table 2).

The physical findings and investigations suggested that the right common carotid artery, previously stenosed, was now occluded, with cessation of embolic amaurosis fugax and the development of low pressure retinopathy.

Comment. This patient also described the attacks of retinal insufficiency in terms of a photographic negative. Some of the attacks were accompanied by simultaneous right hemisphere dysfunction suggestive of focal epilepsy.

DISCUSSION

These four patients suffered from extensive occlusion of the major arteries arising from the aortic arch. In Cases 1 and 4 the cause was severe atherosclerosis and in Cases 2 and 3 the pathology was inflammatory of a type encountered most frequently in young oriental females (Takayasu's arteritis). All patients suffered from attacks of visual loss of retinal origin and in Case 3 the retinal condition had progressed to complete blindness from vitreous haemorrhage and retinal detachment. Case 2 developed permanent impairment of vision due to optic nerve ischaemia on one side. In addition, all patients had attacks of temporary reduction in cerebral perfusion either localized (Cases 1 and 4) or generalized (Cases 2 and 3).

The patients illustrate the compensatory mechanisms in the retinal circulation which accompany a progressive reduction in retinal perfusion pressure, the various factors which provoke temporary loss of vision and the consequences which follow when compensation becomes inadequate.

Compensatory Mechanisms

These comprise both morphological and physiological changes. When a major extracranial artery is occluded there is an immediate increase in flow through the other large arteries and a slow development of collaterals to bypass the occlusion.

For the carotid arteries this leads to enlargement of existing small arteries, usually muscular branches of the costocervical, thyrocervical and internal mammary trunks. A prominent collateral is the ascending cervical artery which develops a communication with branches of the external carotid and with the vertebral artery. In the present Case 3, where both carotid and subclavian arteries were occluded, the entire cerebral and brachial blood supply was derived from the upper intercostal arteries.

In spite of this growth of collateral vessels the perfusion pressure in the cerebral and retinal arteries remains low. This brings into play the autoregulatory mechanism in brain and retina leading to vasodilatation and to a reduction in the peripheral resistance. The efficiency of this mechanism is attested to by the relatively normal levels of cerebral blood flow in our patients in spite of the occlusion of multiple extracranial arteries and with grossly reduced perfusion pressure as measured by ophthalmodynamometry.

Visual Symptoms during Temporary Insufficiency

The symptomatology of ocular insufficiency may differ from that of other varieties of amaurosis fugax due to embolism. In the present Case 1, for example, the onset was less rapid, visual loss developing over minutes rather than seconds; surroundings appeared excessively bright (dazzling, too contrasty) with the affected eye. Although visual acuity was little altered during an attack, the patient had difficulty in reading because of the dazzling effect of the white paper. Recovery also took place gradually. Temporary visual loss of this type has been noted previously in patients with extensive extracranial atheroma (Furlan *et al.*, 1979) and in giant cell arteritis where there may be a similar state of critical retinal perfusion (Hollenhorst, 1967). In our other patients the symptoms were less clearly described. Case 2 described visual loss in terms of a grey mist moving laterally across the field of one eye. On a number of occasions the field appeared fragmented with some scattered areas of blurring. Case 4 also described fragmentation of the central field and a closing in of the periphery.

Mechanisms of Transient Ischaemia

Our patients all exhibited prominent visual symptoms of retinal origin and in the early stages these were intermittent, indicating a temporary failure of retinal homeostasis. These occurred under various conditions.

1. *Minor reductions in systemic blood pressure.* Rapid postural changes provoked visual loss in Cases 2 and 3 and loss of consciousness coming on after standing or after walking rapidly for a short distance.

2. *Rise in venous or intraocular pressure.* Transcapillary pressure gradient can be reduced by venous, intraocular or intracranial hypertension. Cases 1 and 2 noted failure of vision occurring on stooping or straining when venous pressure rose.

3. *Stealing or diversion of blood.* The unusual feature of Case 1 was the regular and predictable occurrence of visual blurring on facial heating, bright light or in warm

surroundings. An attack could regularly be provoked in this way. Ophthalmodynamometry performed during facial heating showed a reduction in perfusion pressure in both eyes but the pressure fell to a lower level on the affected side.

It has been suggested that the dazzling effect experienced by some patients on exposure to sunlight might be due to a failure of the retinal blood supply to meet an increase in metabolic demands with a consequent delay in the resynthesis of visual purple (Furlan *et al.*, 1979). Investigations on Case 1 permit no definite conclusion on this point; a photostress test failed to show any difference between the two eyes such as might be expected if there were interference with the metabolic activity of the photoreceptors. In addition the electroretinogram, showing attenuation of the b wave, was more consistent with a disturbance in the inner retinal layers (including ganglion cells) than in the outer layers (including photoreceptors).

It may be that the critical event producing retinal insufficiency in Case 1 was a fall in retinal perfusion pressure and blood flow as a result of diversion of blood to a dilated external carotid capillary bed, rather than an increase in retinal metabolic requirements.

Low Pressure Retinopathy

Our patients exhibit most of the ocular features described by Kearns and Hollenhorst (1963) as a venous-stasis (or low-pressure) retinopathy. The earliest change is a venous distension with slight irregularity of walls best seen on fluorescein angiography. This is followed by the appearances of blot haemorrhages and microaneurysms in the retinal periphery and by leakage of fluorescein from small venules. Retinal arteries appear normal at the disc but collapse immediately at the lightest pressure on the globe. Slight irregularity of calibre of small arteries may be seen. Later there may be features of anterior segment ischaemia (Dowling and Smith, 1960; Uyama and Asayama, 1976) not seen in our patients but presumably present at some stage in Case 3. These consist of rubeosis of the iris, neovascular changes in the anterior chamber, secondary glaucoma and cataract formation. In the final stage the peripheral retinal arteries may become obliterated and arteriovenous anastomoses may be formed at or near the optic disc; recurrent vitreous haemorrhage leads to retinal detachment and permanent loss of sight.

These changes, which resemble those of diabetic retinopathy, retinal vein occlusion and caroticocavernous fistula, are a consequence of reduced retinal perfusion and hypoxia; leakage of fluorescein indicates there is damage to the endothelium of retinal veins and at a later stage there is new vessel formation and haemorrhage. In low-pressure retinopathy and in caroticocavernous fistula the changes tend to occur in the retinal periphery whereas in diabetic retinopathy and venous occlusion the posterior pole is more affected. Early signs of low-pressure retinopathy have been detected in 20 per cent of patients with internal carotid artery occlusion and may improve after external/internal carotid bypass (Kearns *et al.*, 1979; Edwards *et al.*, 1980). More advanced retinopathy with microaneurysm formation and arteriovenous shunts tends to occur where both external and internal carotid arteries are narrowed or occluded and in this case transcranial bypass is no longer practical.

Cerebral, Brachial and Other Symptoms

A striking feature of our patients was the occurrence of visual attacks without any symptoms of cerebral ischaemia and it seems that the eye is a more sensitive index of hypotension than the brain. Only Case 3 suffered syncopal attacks and these only began when she was virtually blind from retinal detachment. The syncopal attacks were also related to standing and to mild exertion, and on some occasions drop attacks (uncontrollable leg weakness leading to sudden falling) occurred without loss of consciousness. Urinary incontinence was a feature of some of these attacks. Case 2 complained of a state of continuous mild confusion and a feeling of lethargy and heaviness of the limbs but no loss of consciousness.

In spite of the absence of detectable pulses and blood pressure in the arms none of our patients noticed weakness or pain on arm exercise and there were no ischaemic changes in the digits. Cases 2 and 4 had pain in the jaw on mastication, a well-recognized symptom in extensive occlusive disease of the external carotid system.

Course and Treatment

Both in the arteritic and in atheromatous types of pulseless disease there is a tendency for the occlusive process to progress and to extend to other arteries. The changes are more patchy in the arteritic type; for instance, in some patients complete bilateral subclavian occlusion may persist for many years with no clinical or radiological evidence of carotid involvement (Strachan, 1964). In other patients extensive obstruction of the descending aorta and renal arteries may cause renovascular hypertension without any symptoms relating to more proximal great vessels arising from the aortic arch. In severely affected patients with retinopathy, hypertension, aortic aneurysm or aortic regurgitation the five year mortality is about 30 per cent (Ishikawa, 1978).

The systemic symptoms of polymyalgia, fever, arthralgia and inflammatory ocular disease, which frequently precede or accompany aortitis, respond dramatically to corticosteroid treatment and the progression of aortitis is also thought to be delayed (Strachan, 1964). Anticoagulant treatment has also been advocated (Burnstein *et al.*, 1957). That corticosteroids do not offer complete protection from advancing occlusive arterial disease is shown by Case 3 where further retinal and cerebral symptoms developed despite continuous steroid treatment (although only a low dose was used) and where histological evidence of inflammation was found in arterial tissue obtained later at operation.

In atheromatous disease there may also be variations in the degree of involvement of extracranial arteries; the left common carotid artery for instance may be found to be widely patent and relatively free of atheroma in the presence of extensive occlusion of the brachiocephalic trunk and left subclavian artery. Early involvement of the proximal internal carotid artery is also a well recognized feature of atherosclerosis at a time when the common carotid artery is apparently unaffected.

The amount of disease at the carotid bifurcation is a point of considerable practical importance since the internal carotid must be patent before a successful aorto-carotid reconstruction can be achieved. In this context, angiography is useful and can often show filling of the carotid bifurcation *via* extensive transcervical collaterals.

Once complete occlusion of the proximal segment of the common carotid and subclavian arteries has developed, arterial reconstructive surgery offers the best prospect of improving the perfusion pressure to brain and retina and of preventing the permanent consequences of episodic ischaemia. If a single carotid or subclavian artery remains patent it may be possible to use this as a starting point for an end-to-side arterial graft connecting to one or more of the diseased arteries above the level of the block. This avoids the more extensive and hazardous approach to the aortic arch which may itself be involved by the disease process. If no major arteries are available a graft may be inserted into the arch. A variety of successful arterial reconstructions of this kind using dacron prostheses have been developed by Japanese surgeons (Kimoto, 1979). Postoperative patency of the graft with immediate relief of intermittent symptoms may be achieved, but the long-term results are still unknown and occlusion at the origin of the graft has been reported.

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ALEXIA WITHOUT AGRAPHIA IN A COMPOSER

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SUMMARY

A 77-year-old composer had a left occipital lobe haemorrhagic infarct giving him a severe reading disturbance with well-preserved writing and without appreciable aphasia. He continued to read music and to compose. His text- and music-reading performance under different conditions suggests that this unusual dissociation was primarily due to four factors. (1) He was unusually talented musically and inferred a great deal about the music he was reading. (2) The symbols of staff music notation are more visually distinctive than the symbols of phonetic language writing systems. (3) In staff music notation, pitch is represented ordinally, and other symbols are also distinguishable by their relative positions and sizes. (4) Music notation can be usefully read by interpreting it acoustically, kinaesthetically or in terms of formal musical concepts; in contrast to written language, it need not be interpreted referentially or in terms of auditory-verbal images. His disorder fits the classic visual-verbal disconnection account of alexia without agraphia and the contemporary view that music involves a family of related but distinct skills probably involving many brain areas in both hemispheres, although different cortical areas make characteristic contributions to different musical behaviours.

INTRODUCTION

The fate of music reading in alexia in appropriate cases could prove useful in testing and elaborating theories of alexia, of reading and of neuroanatomical specialization. For the musically literate, music reading, like language reading, involves a familiar visual symbol system, fine motor activity, sequential material, visual-auditory associations, visual-verbal associations and visual-motor associations. Many of these aspects can be more or less selectively evoked by varying the music reading task.

The effects of brain damage on music reading abilities have been reviewed by Henschen (1920) and Feuchtwanger (1930), and discussed by Henson (1977) without review of the literature. In addition, some reviews of the amusias discuss the problem (Edgren, 1895; Probst, 1899; Ingegnieros, 1906; Dupré and Nathan, 1911; Ustvedt, 1937; Wertheim, 1969; Benton, 1977; Gates and Bradshaw, 1977), as do some reviews of the alexias (Bastian, 1898; Holmes, 1950; Benson and Geschwind, 1969; Levin and Rose, 1979). A contemporary review of the case literature was presented by Judd (1979) and by Judd *et al.* (1980) and is summarized in the Table.

[*Text continued on p. 438.*]

TABLE SUMMARY OF MUSIC READING CASES

										Reading					Writing	
										Language			Music			
Author	*Background*	*Aetiology*	*Lesion*	*Course*	*Hemiplegia*	*Hemianaesthesia*	*Hemianopia*	*Aphasia*	*Amusia*	*Letters*	*Words*	*Numbers*	*Naming*	*Performing*	*Language*	*Music*
Music reading 'better' than language reading																
Anton, 1888	Violinist	Stroke ?		Improving	—	— ?		*	—	*	*			—	*	
Assal, 1973	Light music, piano, bass	Stroke	L T	Stable at testing	—	—	—	**	—	*	*		**	—	**	—
Assal and Hadj-Djilani, 1976	Farmer	Haemorrhage	L AG	Stable at testing	—	—	—	*		—	*		— ?		*	
Bernhardt, 1872		Stroke ?		Stable	** R		** R	* ?	— ?	**	**	**	*	— ?	— ?	
Bouillaud, 1865	Composer	Stroke ?		Stable				**	— ?		— ?	— ?		—	**	—
Casey and Ettlinger, 1960	Theatrical entertainer	Haemorrhage	L O	Transient	—	—	** R	—		**	**	**	* ?	— ?	**	— ?
Hinshelwood, 1902	Educated	Syphilis		Recurrent transient				* ?		— ?	**	—	— ?	— ?		
Hinshelwood, 1917	15-year-old pianist	'Cerebral disease'		Stable ?							**			—		
Ingham and Nielsen, 1936	Amateur musician	Glioma, surgery	L T	Stable, fatigues	—	—	—	**	— ?	*		— ?		— ?		
Luria *et al*, 1965	Composer, professor	Strokes	L TP	Stable at testing	* R	* R	—	**	—	— ?	*	—		— ?	*	— ?
Oppenheim, 1888	Violinist			Slow onset, stable		**	**	**	* ?					*	**	*
Proust, 1872, Case 1	Good musician							** ?	* ?						** ?	— ?
Proust, 1872, Case 2	Intelligent, musical	Stroke ?			** R			**	* ?	* ?	* ?	* ?	— ?	— ?	**	— ?
Souques and Baruk, 1926	Piano teacher	Stroke	L T AG	Uncertain	—	—	—	**	**	**	**	— ?		* ?	**	* ?

Music reading and language reading equally impaired																
Brust, 1980, Case 1	Voice student, piano, guitar	Tumour, surgery	L TP	Stable at testing	* R	** R	** R	*	—		**		**	**	**	**
Brust, 1980, Case 2	Professional jazz bassist	Haemorrhage	L TP	Improving	—	—	—	**	**		**	— ?	**	**	**	**
Dejerine, 1892	Businessman, singer	Stroke	L O S	Stable at testing	—	—	** R	—	—	**	**	—	**	**	—	* ?
Dorgeuille, 1966, Case 5	Former violinist	Angioma, surgery	L TPO	Stable at testing	—	—	** R	**	— ?	**	**	**		**	*	
Dorgeuille, 1966, Case 22	Keyboards, singer, violin	Glioblastoma	L T	Progressive	—	—	—	**	*		*			*	**	**
Fischer, 1867	Composer, teacher				** R	—	—	**	* ?	** ?	** ?		** ?	**	** ?	*
Frankl-Hochwart, 1891	Merchant, violinist	Syphilis ?		Recurrent	** R			**	* ?		* ?			**	**	**
Holmes, 1950	Physician	Stroke ?		Stable at testing	—	—	** R	—		**	**	—	** ?		—	
Jellinek, 1956	Popular singer, guitar, piano	Tumour, surgery	L F	Stable at testing	** R	—	—	**	**	** ?	** ?	** ?	** ?	** ?	**	
Levin and Rose, 1979	Drummer	Meningioma, surgery	L O S	Stable at testing	—	—	** R	* ?	— ?	**	**	**	** ?	** ?	—	
Potzl, 1927	Businessman	Stroke ?		Stable at testing	* R	** R	** R	* ?	— ?	**	**	* ?	* ?		— ?	
Language reading 'better' than music reading																
Brazier, 1892	Piano teacher	Migraine		Transient	—	—	—	—	* ?	—	—	—		**		
Charcot, 1886, Case 1	Professor of music	Syphilis		Progressive	—	—	—	—	—				** ?			
Charcot, 1886, Case 2	Trombonist	Syphilis		Progressive	—	—	—	—	*						— ?	** ?
Dorgeuille, 1966, Case 12	Chorister, sight-singer	Thrombotic stroke	R FTP ?	Stable at testing	* L	* L	—	*	*	—	—	—		**	* ?	* ?
Dorgeuille, 1966, Case 16	Singer		L T ?		* R	* R	—	—	*		—			*		
Dorgeuille, 1966, Case 24	Former violinist		L T ?		—	** R	* R	*	**		—	**	*		*	— ?
Finkelnburg, 1870	Teacher, violin student	Haemorrhage	R insula, striatum	Transient	* L			*						*	*	*
Jossman, 1927	Teacher, violin, voice	Stroke		Stable at testing	* L	* L	—	—	**				* ?	**		—
Proust, 1866						—							** ?	** ?		—
Wurtzen, 1903	Violinist	Stroke		Stable at testing	* L	** L	—	—	**				— ?	** ?		

** = severely impaired. * = mildly impaired. – = unimpaired. ? = poorly described or tested. L = left. R = right F = frontal lobe T = temporal lobe. P = parietal lobe O = occipital lobe S = splenium AG = angular gyrus

Although the case literature is reasonably extensive, it is still difficult to draw definitive conclusions, mainly because what has counted as music reading varies widely from case to case. Tests used have included naming notes, pointing to symbols named, recognizing melodies from notation, sight-singing, instrumental sight-reading, reading familiar music on an instrument, identifying errors in the examiner's playing and even writing or copying music. Most often a single type of test is presumed to test all music reading. Some authors rely only on the patient's report, while others report only that music reading was preserved or impaired without elaboration. The examination of other musical skills is similarly uneven. Most authors also fail to take an adequate history of training, skills and habits in music reading.

Psychology of Music Reading

One of the major reasons for the frequent inadequacies in the case literature on music reading is the lack of an adequate psychology of music reading. The following brief review highlights some of the most important features of music reading in comparison with text reading (for further details, *see* Judd, 1979; Judd *et al.*, 1980).

Music and language notation systems share the feature of a linear representation of the time dimension on the page. For language this representation is only ordinal (further to the right means later in time), but for staff music notation it is roughly intervallic (the space to the right of each note is proportional to its duration). Most of the language and music notation systems in widespread use today also share to some extent the feature of being phonetic—loosely, each symbol stands for a component sound or the actions necessary to produce that sound. In addition, most music notation systems currently in use, including the widespread staff notation system, share the feature of a linear representation on the page of another dimension, namely, the pitch of the musical notes. Thus, while the phonetics of language writing systems is nominal with different arbitrary symbols standing as the written 'names' of different speech sounds, the 'phonetics' (actually 'diastematics') of staff music notation is in part ordinal and in part intervallic, with notes 'higher' in pitch being represented proportionately higher on the page.

As with most language writing systems, music notations are usually hybrids of phonetic (sound/gesture symbols) and ideographic ('idea' symbols) systems. In staff music notation the many ideographs (for example, clef signs, repeat signs, key and time signatures, bar lines, etc.) play a more important role than do the ideographs in written English (for example, #, %, &, ?, +, 1, 2, 3, etc.). While they can be represented in words, they represent complex ideas about the music or the music reading process at many levels. For instance, bar lines have little if any easily definable representation in sound; they represent instead a way of thinking about the span of time in which the music takes place. Repeat signs, first and second endings, etc., indicate how to read the piece for performance. Clef signs, staff and ledger lines and tempo indications all establish a frame of reference for the phonetic symbols.

Gibson and Levin (1975) have reviewed the graphic features of language writing systems. Most of those features also describe most music notation systems, but two major differences need to be noted. Most language writing systems have gaps that mark graphic and linguistic units. But in staff music notation most of the phonetic symbols are tied together visually by the lines of the staff and the note stems. Most language writing systems have symbols of roughly similar size, but the symbols of staff music notation vary greatly in their size.

Research in the psychology of music reading has been largely confined to mature readers sight-reading staff notation while playing the piano (Sloboda, 1978). These subjects typically read several (3 to 11) notes ahead of what they are playing, just as mature text readers read several words ahead of what they are saying when reading aloud. They use the structure of the music and the structure of the notation to help them read patterns of notes and they infer quite a bit about the music on the basis of their knowledge of musical structure. In fact, they often fail to notice printer's errors and play instead the correct notes inferred from the context.

Review of Cases of Musical Alexia

Despite the many problems of available case reports, several tentative patterns emerge. First, many different types of disorder can result in impairment of music reading for different reasons (Feuchtwanger, 1930; but *see* Benton, 1977, and Ustvedt, 1937).

Secondly, there are no convincing cases of isolated disturbances in music reading (Benton, 1977). Those cases in which musical alexia is not accompanied by text alexia seem attributable to a more general musical disturbance (*see* Finkelnburg, 1870; Würtzen, 1903; Jossman, 1927; Dorgeuille, 1966) or else the phenomenon was transient and poorly examined and described (Charcot, 1886; Brazier, 1892). Nevertheless, the possibility of such a syndrome cannot be ruled out. If, for instance, a musical alexia without agraphia were to result from a splenial and right occipital lesion in individuals with certain music reading styles, it might not get reported, given the rarity of such lesions, the low musical literacy rate, and the small likelihood that the affected individuals would seek medical attention or receive neurological recognition.

Thirdly, Benson and Geschwind (1969) appear to have been correct in concluding that in most cases of alexia without agraphia, music reading is also disturbed (*see* Dejerine, 1892; Pötzl, 1927; Holmes, 1950). In two case reports claims are made that appear to be exceptions to this rule. Casey and Ettlinger (1960) reported the case of a 45-year-old, right-handed male theatrical entertainer with a left occipital haemorrhage, right hemianopia and alexia. They claimed that their patient showed 'preserved music reading' in that he was able to apply a rhyme to the positions of notes on the staff in order to name the notes, and to read rhythms that he had just written in an idiosyncratic notation. The former test compares to an ability to count lines, while the latter is confounded by the memory of what he had just heard and written and is in any case questionably related to reading staff music notation.

Assal and Hadj-Djilani (1976) reported the case of a 58-year-old, right-handed male farmer with a haematoma beneath the left angular gyrus. He had no visual field defect and little difficulty with language function except that his reading was moderately impaired. His 'perfect' music reading apparently refers to naming musical symbols and notes. Thus these cases do not provide clear examples of alexia without agraphia with preserved music reading.

But again, caution is in order. The music-reading backgrounds of the patients described are unimpressive or poorly described and the testing is inadequate. Alexia without agraphia, musical literacy and adequate testing are all rare and the appropriate co-occurrence of these factors may not yet have come about.

Fourthly, music reading can be preserved in the face of a language reading disturbance if there is a more general language disturbance present (*see* Bouillaud, 1865; Hinshelwood, 1917; Souques and Baruk, 1926; Ingham and Nielsen, 1936; Luria *et al.*, 1965). In other words, if an alexia is secondary to an aphasia, music reading may be preserved. This is especially true if the music reading task does not involve a verbal component. For example, Assal (1973) reported on a 64-year-old, right-handed male clerk who was a light music pianist and string bass player. He had a severe Wernicke's aphasia from an embolic stroke. His language reading was poor, yet he could sight-read accurately at the piano, and he took up a musical career. He was unable to name musical symbols.

In sum, it appears that aphasics may have poor text reading with preserved music reading, amusics may have poor music reading with preserved text reading, and patients with visual-lexic disturbances may have both text and music reading impairments with other language and music functions preserved, but strong dissociations between music and text reading without major disturbances of other aspects of language or music have not been reported.

The case presented here is of a composer with alexia without agraphia. We have attempted to avoid some of the procedural limitations of earlier studies, and have determined the effects of his illness on several different forms of music reading behaviour. We have also used his disability to examine some of the differences between music and language reading.

CASE HISTORY

Because this case has been reported previously in detail by Levine and Calvanio (1978, their subject R.T.) and by Judd (1979) and Judd *et al.* (1980), only a brief clinical history will be given here.

B.L. is a 77-year-old, right-handed composer-conductor and retired professor of music in previously excellent health who was conducting an orchestra when he felt as if he had been 'hit in the head'. The next morning he was confused with unintelligible speech and faltering gait. He was admitted to Massachusetts General Hospital that same day.

Neurological Examination

The patient had a right homonymous hemianopia. Corrected visual acuity was 1/5 normal at 2 ft viewing distance. The range of eye movements was full, but optokinetic nystagmus was markedly diminished with targets moving to the patient's left (that is, the acute phase of nystagmus was absent to the right). There was some slight right facial weakness, but normal limb strength and somatic sensation. A slight right hyperreflexia and positive right Babinski sign were present.

Lumbar puncture revealed yellow-pink CSF. Skull x-rays were normal. A CT scan four days after admission showed an area of increased density consistent with a left occipitotemporal haematoma (fig. 1).

At four days post-onset the patient was alert and showed marked word-finding difficulty and frustration. He spoke slow and purposeful complete grammatical sentences with self-corrected literal and verbal paraphasias. Articulation was unimpaired except for occasional stuttering. He was unable to perform one-step verbal commands, but he repeated them clearly. He could not identify any printed letters or words and could write only his name.

In summary, the patient suffered a haemorrhagic infarction of the left occipitotemporal area producing an aphasia characterized by a mild degree of fluently abnormal speech with mild to moderate disturbances in comprehension and repetition, a total inability to identify letters and words, and a dense right hemianopia. The aphasia and agraphia cleared rapidly except for a mild residual anomia and occasional paraphasias so that the patient was left with hemianopia and other features of the syndrome of alexia without agraphia.

Other Investigations

Beginning one month after his stroke, B.L. was a subject in an investigation by Levine and Calvanio (1978) (their subject R.T.). They studied letter recognition and naming with tachistoscopic presentation. B.L.'s duration threshold for single letter naming was only slightly longer than that of normal controls. An aftercoming masking pattern impaired his single letter naming only slightly more than for normal subjects. Yet when presented with 3 letters he was usually unable to name them all, even with up to 5 s exposure. He was successful in naming single pre- but not post-designated letters in an array of 3. He named letters better if they made an English word than if they did not, regardless of whether or not he was expecting a word. Besides omissions, his errors in all conditions were mostly morphological, that is, he named letters that were similar in shape to the targets.

PRESENT INVESTIGATION

The present authors saw B.L. for three months beginning one year after his stroke, and again at eighteen, twenty-four and thirty months.

Neurological Status

B.L.'s dense hemianopia persisted and he complained of some double vision on downward gaze. Sensation, strength and reflexes were all normal.

Neuropsychological Examination

The patient was attentive, cooperative, and well aware of his difficulties. He was slow at most tasks, but persistent and perfectionistic. He fatigued noticeably over several hours' testing, so sessions were frequent, short and varied.

He reported that he had noticed a definite improvement in the past few months and had returned to composing. He said he frequently lost articles, and could not search for them very well. He had a tendency to neglect things on his right.

Intelligence. B.L. achieved a WAIS Verbal IQ of 117, reflecting his high educational level and lack of serious aphasic impairment. He showed a difficulty in dealing with numbers and with short-term memory (Arithmetic scaled score of 5,

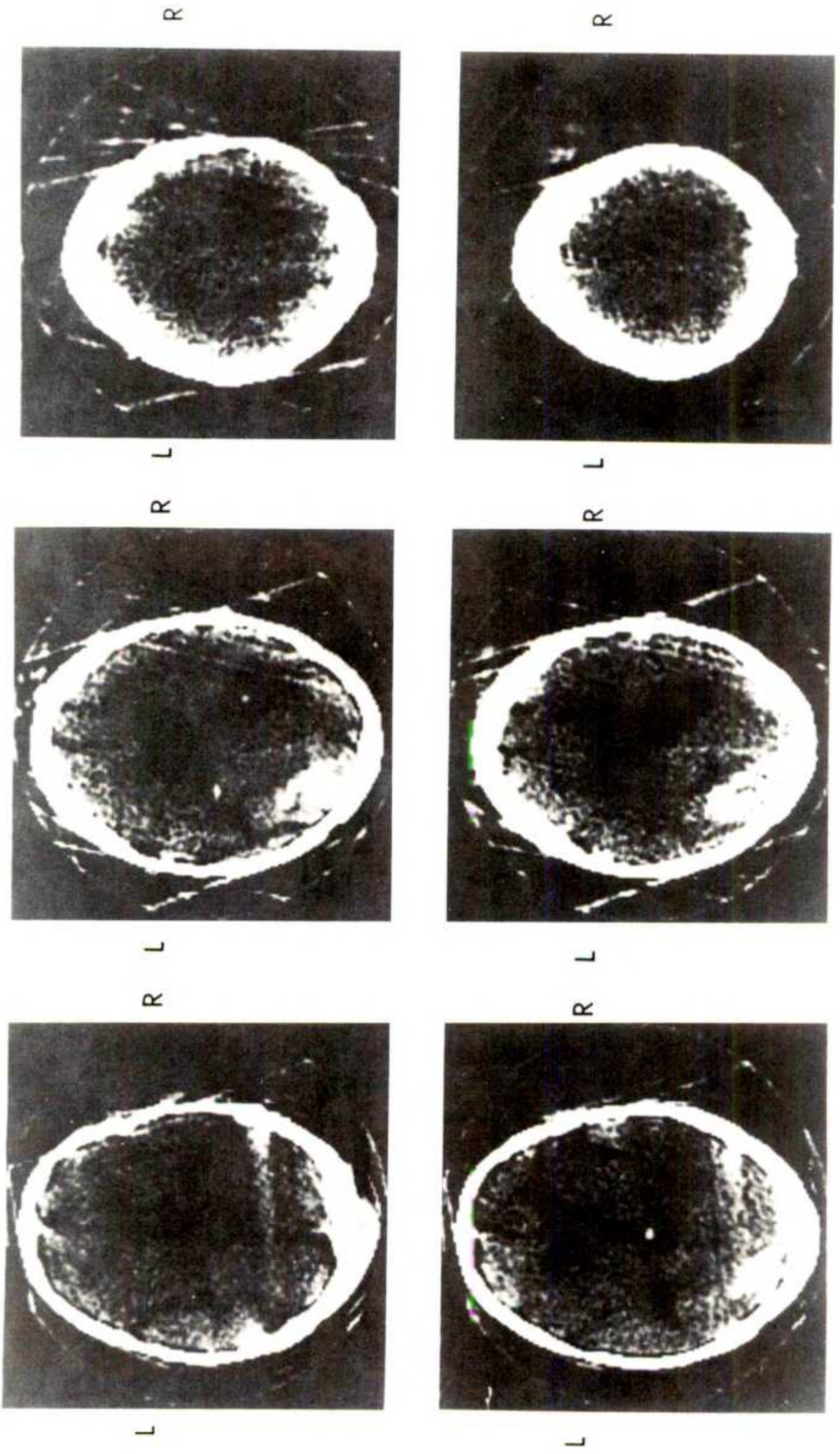


FIG. 1. Unenhanced cranial CT scan of B.L. showing left occipital haematoma.

Digit Span of 6 forward and 4 backward). He achieved a Performance IQ of 78, reflecting slowed performance and difficulty in keeping track of the visual stimuli. Nevertheless, he showed good strategies on visual-constructive tasks, and he completed all the Block Designs and Objective Assemblies correctly and only once required more than twice the allotted time to do so.

Memory. B.L. achieved a Wechsler Memory Quotient of 89 (using norms for 60 to 65-year-olds), showing a mild impairment in learning new material. After a 20 min delay he had good retention of learned verbal material, but poor retention of learned visual material.

Praxis. The patient responded promptly and accurately to all requests to mime various activities. However, in imitating nonrepresentational gestures he sometimes used the wrong hand or wrong finger.

Visual-spatial Abilities. The Hooper (1958) Visual Organization Test consists of 30 pictures in which a line drawing of an object has been cut into 2 to 5 pieces like a jigsaw puzzle. The subject's task is to name the object. B.L. got 24 correct, a very good performance for his age.

B.L. performed completely normally in identifying a set of subjective contours (Kanizsa, 1976). Subjective contours are displays that create in the viewer the perception of a contour or form not actually present in the stimulus (fig. 2). Perceiving subjective contours involves integrating information from several figures separated on the page, and has been reported to be severely impaired in visual agnosia-simultanagnosia (Wapner *et al.*, 1978).

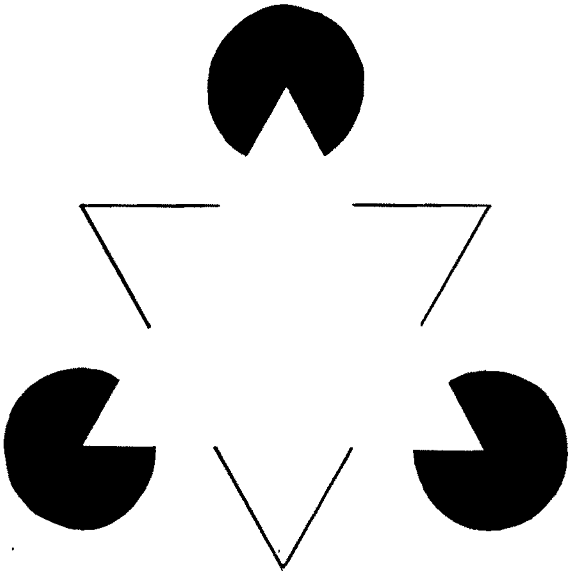


FIG. 2. An example of a subjective contour.

On the Boston Diagnostic Aphasia Examination (BDAE) Supplementary Tests (Goodglass and Kaplan, 1972), B.L. performed adequately on 4 of 6 drawings to command. He performed normally on copied drawings, on reproducing stick designs from immediate memory, on right-left orientation, in clock-setting and on pointing to named locations on an unlabelled map. He showed moderate impairments on all verbal and nonverbal modes of finger gnosis testing. When questioned he noted that he sometimes made minor errors in playing the wrong chord or putting his hands, especially the right hand, at the wrong place on the piano. He performed poorly on written arithmetic.

Neurolinguistic Examination

B.L.'s spontaneous speech was fluent but mildly paraphasic and circumlocutory. His repetition was normal. Auditory comprehension was mildly impaired, most noticeably for single words and for body-part identification. He performed better with comprehension material involving longer phrases and sentences, apparently benefiting from redundancy.

He was quite good at naming objects from their descriptions. He was slower at naming pictures of objects and made several verbal paraphasias, and possibly perceptual errors. Colour naming was good. He made frequent verbal paraphasias in trying to name body parts.

Reading. He was severely impaired at all levels of reading. Of all reading skills tested, he was best at comprehension of oral spelling and letter reading. For instance, he got all 8 of the Comprehension of Oral Spelling items on the BDAE correct which include difficult words such as 'whiskey'. On the Visual Confrontation Naming Test he named all 6 letters correctly within 3 s each. He named 27 out of 33 upper and lower case letters scattered on a page correctly in 300 s.

Despite his good performances on these tests, he was unable to put these skills together to produce adequate word reading. He was able to recognize a few words without analysis, especially shorter ones and words attempted at the beginning of his reading efforts. Failing this he named each letter, tracing with his finger those he had trouble recognizing, trying to recognize the word from its oral spelling. He frequently failed because he misnamed the letters or because it took him so long to name them that he forgot some. For instance, in trying to read 'HAMMOCK' he spelled 'H-A-R-R-O-C-H' and only got the word correct after a second try, taking 20 s.

On the BDAE he was unable to match short words and letters to their equivalents in other English alphabets, namely, upper and lower case and cursive. His errors suggested visual confusions: 'B' and 'd', 'dog' and 'BOY', 'pal' and 'gal' (cursive). He showed other apparently visual confusions pointing to written words from their oral names ('shop' for 'ship', 'beer' for 'book', 'whip' for 'with'). He was unable to match words to pictures without reading aloud.

When he attempted to read prose the above patterns were present, but he also showed perseveration and contextual guessing, such as (the BDAE stimulus sentences are in parentheses) (You know how.) 'You know how'. (Down to earth.) 'How to eat . . . How to earn . . . Down to earth.' (I got home from work.) 'I do . . . I dot . . . I have hope for . . . from . . . I hop down from work.' (Near the table in the dining room.) 'Fear the table in the dining room . . . F-E-A-R.' (They heard him speak on the radio last night.) 'She feared him . . . She heard him speaking of him in the reading room.' (Limes are sour.) 'L-I-M-E-D . . . something to do with soup. Lines are after soup. S-O-U-P soup.' This much took 10 min.

He neither reported nor displayed any evidence of extracting any semantic content from written words without being able to read them aloud. He could not categorize written words semantically nor answer questions about their meaning without reading them aloud.

His number reading was worse than his letter reading, and he especially confused 5, 6, 7 and 9.

He was very distressed by his reading disorder and practised reading daily in an attempt to recover. He wore mild magnifying lenses over his trifocals when attempting all reading and writing whether of language, numbers, music or pictures. His claim that larger letters and notes were easier for him to read appeared to be true.

Writing. His handwriting was legible, but it was painstakingly slow and showed occasional distortions, substitutions, omissions and doublings of letters. Except for these errors he could write whatever was requested including numbers, letters, words, and sentences to dictation, the names of pictured objects and descriptions of pictures. The results of his attempts to copy were similar to his spontaneous and dictation writing, except that he showed some of the contextual guessing and perseveration typical of his attempts to read prose (*see* fig. 4).

Neuromusicological Examination

Before his stroke B.L.'s vocal and keyboard skills were adequate for teaching and composing, but his public performance was largely limited to conducting concerts of his own compositions. He enjoys an international reputation as a composer, primarily of choral works entirely in the tonal system and with a very lyrical style. He composed with frequent reference to the keyboard and often improvized for his own pleasure, yet much of the compositional process also took place away from the keyboard, for example, at the blackboard in front of his classes. He had an intimate knowledge of tonal theory and was completely literate in music. He was an experienced proof-reader, could sight-sing, sight-read at the piano and read a score 'hearing it in his head'. He did not have absolute pitch.

Critical Perception. On our examination his perception of music seemed intact. His pitch discrimination was very good, and he was able to detect slight changes in tempo and errors in performance. He criticized with great sensitivity a taped performance of one of his compositions, commenting accurately on tempo, attacks, dynamics, tone quality, intonation and emotional interpretation. He resumed rehearsing and conducting his own works one year after his stroke, reportedly quite successfully.

Production. The following descriptions apply both to reading and performing by ear. He sang with poor tone quality (apparently a premorbid trait), expecially in the lower register, but he was musically accurate, with good expression.

His piano playing was slowed and he complained of displacing his hands a note or two on occasion, especially his right hand. Though scales and exercises were performed adequately, there was often some groping for keys. On easy familiar material he played correctly and expressively, but on more difficult familiar material he was slow and made many mistakes. By his own judgement this was significantly worse than before his stroke, but since he played very little for the six months following his stroke, some of this may have been due to lack of practice. During our period of observation he played often and we noted distinct improvement over time.

He generally conveyed a musical intention as he played. He often omitted less important lines and chords to maintain the musical flow. On the other hand, on very conventional or familiar music he sometimes added characteristic harmonies, ornaments and internal lines. He was able to perform free improvization appropriately and creatively with few errors and a good sense of form, although his playing was necessarily at a slow tempo.

Reading. B.L. used music reading skills effectively in a wide variety of contexts. He read scores at the piano for pleasure, read and worked on scores of his works in progress, checked proofs from his publisher, read (without playing) and commented on scores of student composers and searched for, found and played specific pieces in his library. He did, however, have some difficulties reading music in these and other contexts. He was unreliable at naming various musical symbols, he was poor at sight-reading unfamiliar, musically unconventional and unpredictable material such as sight-reading exercises, he tended to lose his place and to omit notes from the right side of the page and he made contextual guessing errors.

He recognized familiar pieces of music quite readily and rapidly from the printed score, even when the words were covered. For instance, on the California Diagnostic Test of Music Achievement, Test 10 (California Test Bureau, 1950), he recognized and named 18 out of 20 familiar folk melodies from the first four bars of their notation. By contrast, he recognized only 2 out of 10 of the printed song titles.

His ability to use individual musical symbols depended upon the task and the stimulus context. At sixteen months poststroke he could name only 1 out of 17 musical symbols scattered on a page, but he pointed to 14 of them correctly given their oral names and wrote 9 out of 10 of them correctly given their oral names. In the context of a musical score, however, he named 7 out of 14 correctly and pointed to 13 out of 14 correctly from their oral names. At twenty-four months poststroke he was given a page with musical symbols, letters and numbers mixed up on it. He named 12 out of 13 letters, 11 out of 15 musical symbols and 6 out of 13 numbers correctly.

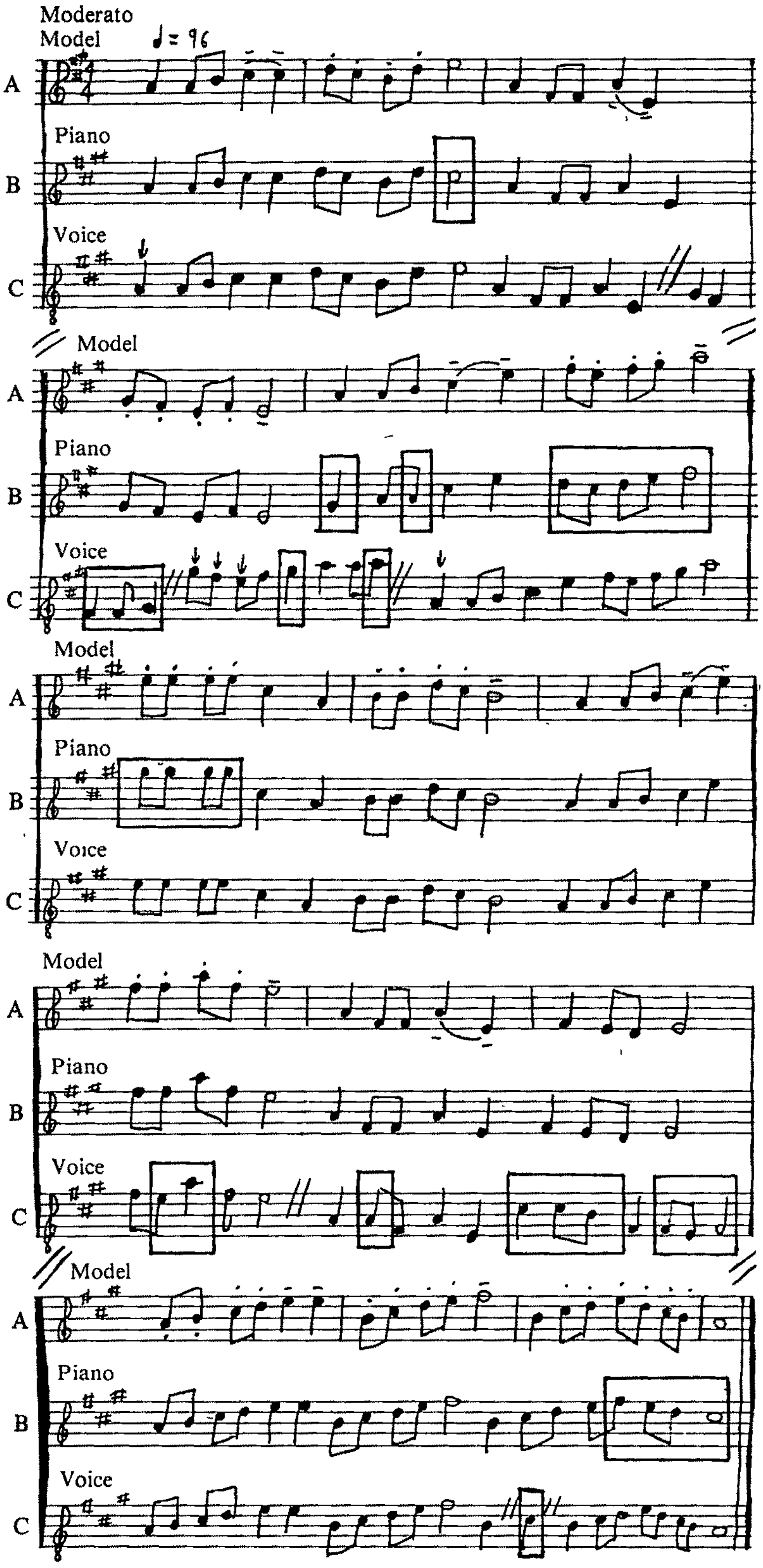
When trying to follow the score of a piece being performed he frequently fell behind, even if the piece was quite familiar. When he did follow the score he was often able to pick out errors of performance. He chose to conduct concerts without the score for fear of losing his place.

In playing the piano he preferred playing from a score to playing by ear, except for works in progress. His playing was slow and laboured, with frequent self-corrected mistakes. He was nonetheless often able to maintain a tempo while playing a melody with harmony and was sometimes able to play two- and three-part counterpoint. Because of his right hemianopia and neglect he sometimes omitted the last few notes on a line. He occasionally lost his place on the page, especially when he momentarily looked at his hands. His pitch errors were most often off by a musical third, suggesting that he was able to recognize whether the note was on a space and not a line, for example, but was unable to recognize which space.

No particular musical aspect of the reading or playing gave him special difficulties—he read melody lines, chords and rhythms accurately, and co-ordinated contrapuntal lines automatically—but the complexity of the task slowed him down and as a consequence the rhythm often suffered. He used 'faking'—in the best sense of the word—in his keyboard music reading. On difficult pieces he sometimes omitted less important inner voices in order to maintain the flow of the music, he sometimes anticipated a chord without actually reading it, and he sometimes regularized a rhythm or a melody. He used memory of specific pieces as a supplement to reading; for example, in his recent composition he played the second verse when reading from the similar music for the first verse. Thus, he seemed to rely heavily on the musical context in reading, as is typical of a skilled and knowledgeable reader (Sloboda, 1978).

His sight-reading of totally unfamiliar material exaggerated these tendencies. On elementary school tests of sight-singing (Bowles, 1971) and sight-reading (Farnum, 1969, playing the violin score on the piano), he 'regularized' the improbable rhythms and melodies (fig. 3). Also, when he made an error of pitch, he sometimes continued to play the next few notes transposed by the magnitude of the original error, suggesting that he was reading more by the relative intervals between successive notes than by the absolute positions of the notes on the staff. His approach to these tests made irregularities in administration necessary, but his performance was poor in comparison with the elementary school music students of the normalization sample.

Writing. When B.L. attempted his first poststroke composition at twelve months, he had great difficulties getting it down on paper and resorted to dictating by playing to an assistant. As they progressed he became able to write down large portions of it himself, but these writings had to be checked for accuracy. A few months later he was able to correct the proofs and make improvements. He complained that he often failed to place his notes properly, for instance, a note intended for a space would wind up on the adjacent line. We therefore made him wide-lined staff paper, which


Moderato
Model
♩= 96
A
Piano
B
Voice
C

helped significantly. Fig. 4 illustrates his music- and text-copying abilities in parallel at fourteen months poststroke.

At twenty months poststroke he wrote a 7 min piece for chorus and orchestra in five weeks with no assistance. Only a dozen errors or so were found in his score, demonstrating that his musical writing at this point was quite functional.

His performance on musical dictation tasks was surprisingly poor, considering how well he wrote down melodies that he composed. At fifteen months poststroke he wrote only one of 5 short (3 to 5 note) melodies correctly, despite his requests for up to 4 presentations of each. The rhythms were generally correct, but he made errors of pitch. Given a 4 bar, 16 note melody, he requested 11 presentations and got it

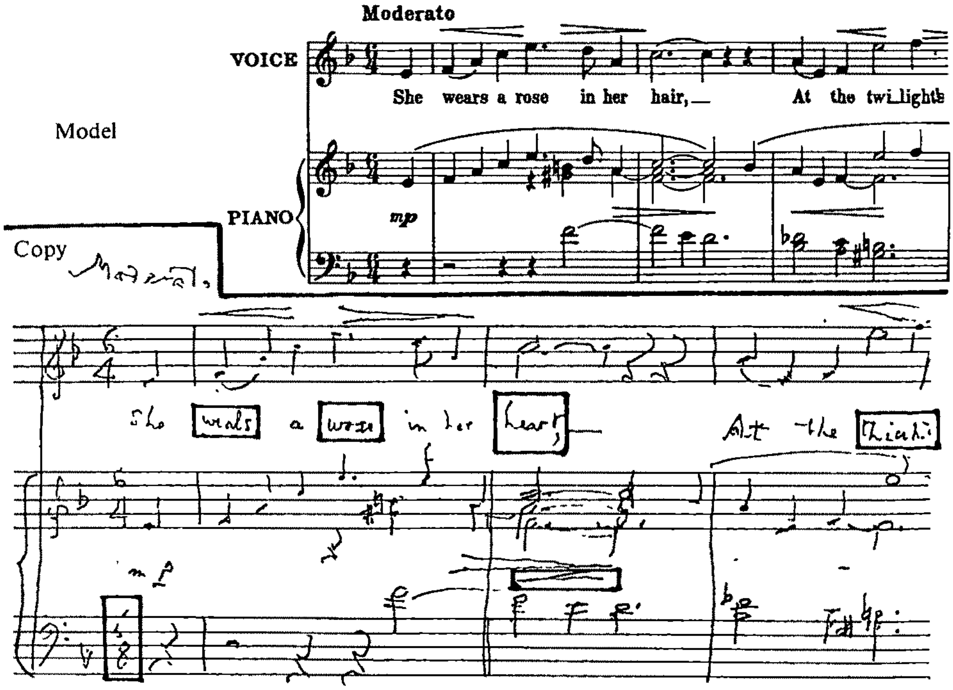


FIG. 4. Music copying by B.L. The model is reduced by 40 per cent. The copy is reduced by 55 per cent. Boxes are drawn around his errors

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FIG. 3 (*opposite*). Music sight-reading by B.L. Line A is a transcription of the original stimulus from the Farnum String Scale (Farnum, 1969) Violin Exercise No. 6. Line B is a transcription of his sight-reading of that exercise on the piano. Line C is a transcription of his sight-singing of that exercise one week later. Arrows in this line indicate the notes on which he reinforced himself with the piano. Boxes indicate errors The octave transposition in the fourth and fifth bars was to accommodate his vocal range.

correct except for three minor omissions. He wrote down 4 chords to dictation flawlessly, but required 3 presentations of each. He made several errors in writing rhythms to dictation on longer items, especially when the barring was not obvious.

Memory. On several occasions we sang a short melody to him and asked him to repeat it. Several repetitions of the model were generally necessary before he got it correct. When asked to recall the melody several minutes later he was unable to, but could recognize it from a multiple choice. By contrast, if we asked him to make up a short melody and sing it, he was then able to repeat that melody immediately and several minutes later. The difference between these two conditions may account for the difference between his ability to write music spontaneously and to dictation. A mild impairment in anterograde musical memory is consistent with his mild anterograde memory impairment in other areas.

Composition. B.L.'s composing skills appeared undiminished. He worked more slowly, could not rely on reading his texts, and relied on the keyboard more than before his stroke because of shortcomings in writing and memory. For these reasons he attempted less ambitious works. Nevertheless, his poststroke compositions have been well received. Independent critics consider them to be as good as his prestroke compositions, but musically somewhat more conservative.

DISCUSSION

We have presented the case of a composer with a severe reading disorder resulting from a cerebral vascular accident. He showed right hemianopia, severe alexia, an ability to read single letters and to read letters by tracing, relatively well-preserved writing ability, spelling and comprehension of oral spelling, and a left occipital lobe lesion as confirmed by CT scan. These signs lead to diagnoses of alexia without agraphia and of semantic alexia. Complicating signs, mostly mild, included diplopia on downward gaze, right visual neglect, anomia, memory impairment, number confusion, body part confusion, agraphia and slowing. While some of these signs may be due to age, they also suggest that his lesion may extend into the left parietal lobe, producing mild symptoms of the alexia with agraphia syndrome. His CT scan results and symptoms are consistent with the classical visual-verbal disconnection account of alexia without agraphia (Benson and Geschwind, 1969; Dejerine, 1892).

B.L. is ideal for a study of music reading. As a composer and professor of music he was well practised in many different ways of reading music. Investigation of his other musical skills showed that aside from slowness, memory difficulties and occasional mild clumsiness at the keyboard with his right hand, he had no specific musical difficulties which might be expected to confound the study of his music reading. He was highly motivated towards reading both language and music.

Despite the many similarities between music and language reading, it is difficult to find the most appropriate ways to compare them. B.L. was similarly impaired at naming the symbols in each system. He made errors in reading short phrases of unfamiliar material in both text and music reading and performed at the elementary school level in both. Much more importantly, though, B.L. could read music well after his stroke and used music reading daily in a wide variety of ways, while he read text poorly and text reading played very little role in his life. Furthermore, Levine and Calvanio (1978) have clearly demonstrated (and we have confirmed) that at least under some circumstances B.L.'s ability to read single letters was greatly impaired by the presence of other letters. But music symbols were generally more accurately identified and more rapidly played in their appropriate context than in isolation on a page.

The differences between B.L.'s music reading and language reading impairments and strategies must at some level indicate something distinctive about the organization of the brain or the nature of alexia, but it is difficult to say at what level. Despite their common features, English text and staff music notation differ at three major levels. They differ graphically in the relative size and spatial placement of the symbols. They differ symbolically in the amounts of phonetic and ideographic representation, in the use of nominal, ordinal and intervallic modes of representation and in the significance of variations in symbol size and placement. They differ functionally in the types of output and processing strategies commonly used.

Our results suggest that all three of these levels of differences between music and text reading play some role in B.L.'s different performances in the two modes. That graphics are important is suggested by his tendency to make errors involving visual confusions. Morphologically similar substitutions were seen in letter identification (for example, O for Q or C, W for V or N, etc., *see* Levine and Calvanio (1978) for a detailed analysis), word identification ('for' for 'from', 'reading' for 'radio', etc.) and note reading (errors of a musical third).

The importance of the symbolic differences between English text and staff music notation is supported by B.L.'s introspection that he read the pitch of each note relative to the pitch of its predecessor (thus relying on ordinal features of pitch notation). This was reflected in his tendency to make errors of transposition by the interval of the initial error.

The importance of the functional differences between music reading and text reading is supported by the fact that he was generally faster and better at performing from music notation than at naming symbols or notes, that is, musical output was better than verbal output with music notation input.

We have done no more than provide some clues to the analysis of the graphic, symbolic and functional levels in pathological dissociations between music reading and text reading, the relative importance of which remain to be determined in future studies. The observation made above, that alexics with well-preserved music reading tend also to be aphasic, also suggests that in these cases functional factors are very important. In Assal's (1973) case, for example, music reading was unimpaired except when a verbal response was required. The importance of symbolic factors (phonetic *vs* ideographic representation) is already clear for language reading in Japanese aphasics in whom a double dissociation is sometimes observed between the ability to read phonetic Kana scripts and the ideographic Kanji script (Sasanuma, 1975), and in Western 'phonemic dyslexics' who can read some words 'ideographically' but not 'phonetically' (Shallice and Warrington, 1981). The roles of graphic and symbolic factors might be elucidated by the study of patients trained in other music notation systems such as guitar, lute or koto tablature, or the cipher systems of elementary education, guitar notation and Indonesian gamelan (*see* Addendum).

It is difficult to find a satisfactory explanation for B.L.'s pattern of deficits. Explanations based on a primary visual defect, a material-specific agnosia, or generally insufficient visual feature discrimination can be excluded (Levine and Calvanio, 1978). Similarly, his alexia cannot be accounted for as a 'simultanagnosia' or impaired Gestalt perception since he performs well on visual perception and construction tasks requiring the integration of separate elements (Levine and Calvanio, 1978) and also exhibits normal perception of subjective contours. Levine and Calvanio suggested that he has an impairment in 'the identification of a compound array consisting of multiple identifiable components, where misidentification of any component will usually impair identification of the array'.

We agree that B.L.'s identification of familiar visual symbols such as letters can be impaired by the nearby presence of other similar visual symbols, as seen in Levine and Calvanio's experiments. However, this characterization appears to us to be incomplete and to some extent an artefact of experiments designed to minimize contextual cues which might facilitate element identification. Levine and Calvanio used upper case letters which give less information about their identities on the basis of the printed context than do lower case letters. Most of their tests used nonwords, but the patient identified almost twice as many letters when words were used. In addition, the patient's reading of lower case connected prose, although quite impaired, was much better than one might have predicted on the basis of his letter and word identification performance, and he displayed considerable inference from context. Finally, in our music reading experiments he was quite capable of using visual context in the identification of elements. It appears likely that context may influence B.L.'s reading and the reading of normals in a qualitatively similar fashion.

While we are unable to give a full explanation of his disorder, we feel that there is some merit in characterizing B.L.'s disorder as a visual-verbal disconnection. This would account for his alexia, his poor naming of objects presented visually as compared to other modalities, and his poor naming of musical symbols in the face of good non verbal identification of those symbols. However, an alternative explanation—that he has mild impairments in visual perception and in naming which are exaggerated when these two tasks are combined in the tasks of reading or naming things presented visually—yields a similar result and cannot be excluded.

Furthermore, neither explanation accounts for his failure to show any semantic substitutions in text reading as is seen in 'phonemic dyslexics'. Clearly, a thorough explanation of this disorder still eludes us.

Our results demonstrating considerable sparing of music reading abilities in a patient with alexia without agraphia are very different from other reports of music reading abilities in alexics without agraphia (Dejerine, 1892; Pötzl, 1927; Holmes, 1950; Levin and Rose, 1979). Although these cases were poorly examined with respect to music, some explanations of the differences are possible. First, B.L. was a skilled music reader with many music reading strategies, while the cases cited above were amateurs with uncertain musical skills (the sole exception may be Levin and Rose's case who was a professional drummer but who may never have learned to read music, or at least pitch notation, well). Secondly, our subject was in practice at reading music up to the moment of the stroke, and he had begun to practise again before we saw him. Most of the cases cited above did not report whether the patient was in practice. (The differences between music reading and text reading in B.L. are not due to practice effects. He had had months of language reading therapy and had practised reading text daily.)

There are, however, precedents in the literature for several of the phenomena that we have observed. Assal and Hadj-Djilani (1976) reported a case of good music reading in an alexic without agraphia. Most of the other reports of sparing of music reading in alexia have used performance as a measure, whereas most of the reports of loss of music reading with alexia have used note- and symbol-naming as a measure. Levin and Rose (1979) reported an effect of improved musical symbol identification in a musical context, and Dejerine and André-Thomas (1912) reported improved nonmusical symbol identification with the addition of context. Bouillaud (1865), Anton (1888), Luria *et al.* (1965) and Assal (1973) all reported cases in which musical creativity was preserved in the face of left hemisphere damage.

Music Writing

Visual feedback is not necessary for writing the cursive script of many European languages, therefore alexia need not necessarily interfere with writing skills. However, visual feedback may be necessary for writing Japanese and other visually complex writing systems. In staff music notation, visual feedback is necessary for writing pitch but not rhythm. Thus, music reading difficulties are likely to be accompanied by difficulties writing the correct pitch but not necessarily the correct rhythm or other symbols. In the present case music writing errors were primarily errors of pitch and faulty symbol placement, while rhythms were generally correct. Similar patterns have been reported in previous cases (Dejerine, 1892; Dorgeuille, 1966, Case 12).

Neuroanatomy of Musical Alexia

Music reading disturbances are often the result of left hemisphere lesions (Judd, 1979). Language reading disturbances are often associated with these musical alexias. Undoubtedly this association is due in at least some cases to a more general visual-perceptual disorder (Martin, 1954), but this explanation probably does not extend to this case. Cases of musical alexia with right hemisphere lesions are generally accompanied by significant amusia (Judd, 1979).

Feuchtwanger (1930), Ustvedt (1937), Barbizet (1972), Benton (1977), Gates and Bradshaw (1977) and others have all taken variations on the position that music involves a family of related but distinct skills probably involving many brain areas in both hemispheres, although different cortical areas make characteristic contributions to different musical behaviours. Increasing evidence suggests that these views are correct. But at the same time it appears unlikely that musical functions will break down simply into Barbizet's (1972) scheme of perception and expression on the right, and of reading, writing, composing, memory and theory on the left. Music reading alone can involve a variety of activities with a number of strategies available for each. We have seen that these activities can be differentially effected by a unilateral brain lesion. B.L.'s symptoms suggest that the left hemisphere is important in naming musical symbols. His use of context and his sight-reading may reflect strategies successfully used by the right hemisphere. It appears likely, then, that the roles of the cerebral hemispheres and various areas within those hemispheres in music reading will depend heavily upon the nature of the activity and the particular history of the patient. This is a discouraging outlook from a research perspective since it makes it much more difficult to compare cases. Nevertheless, the amusias also provide a research opportunity not readily available in the aphasias, allowing us to study the effects of training and experience on the cortical organization of behaviour.

ADDENDUM

The first author has had the opportunity to examine Brust's (1980) Case 1, an alexic with agraphia with 'phonemic alexia'. Brust's findings were confirmed and it was also noted that the patient was able to play guitar chords from tablature or from the printed letter names of the chords (a well-practised premorbid skill) although she was unable to name the letters.

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SELECTIVE OLFACTORY DEFICITS IN CASE H.M.

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SUMMARY

A variety of olfactory capacities were evaluated in H.M., a patient with bilateral medial temporal lobe resection. He demonstrated normal performance on a battery of tests of odour detection, discrimination of intensity, and adaptation. In striking contrast, H.M. was unable to discriminate or identify odours in same-different discriminations and in matching-to-sample tasks. Although he could name common objects using visual or tactile cues, he could not identify them by smell. These results indicate that the perceptual phenomena of odour detection and discrimination are dissociable by cerebral damage, and that structures in the medial temporal lobe play a critical role in odour discrimination.

INTRODUCTION

An increasing body of evidence indicates the involvement of both the frontal and temporal lobes in odour perception. Impairments in odour quality discrimination have been observed in rats and monkeys with lesions of the orbitofrontal cortex or its associated mediodorsal thalamic nucleus (Tanabe *et al.*, 1975*b*; Eichenbaum *et al.*, 1980; Sapolsky and Eichenbaum, 1980; Slotnick and Kaneko, 1981), and in monkeys with bilateral ablation of the anterior parts of the temporal lobe (Brown *et al.*, 1963). Olfactory disorders have also been described in several neurological conditions, including Korsakoff's disease, which damages the mediodorsal thalamus (Victor *et al.*, 1971), lesions of the orbitofrontal cortex (Jones *et al.*, 1975; Potter and Butters 1980), and unilateral temporal lobectomy (Rausch and Serafetinides, 1975; Eskenazi *et al.*, 1981). These behavioural observations parallel recent revisions in the delineation of primate olfactory pathways. The olfactory tract projects centrally by three routes: (1) the medial olfactory stria, which contains no afferent fibres but does support a centrifugal pathway; (2) the lateral olfactory stria, which projects to the pyriform, periamygdaloid, and entorhinal cortices of the uncus of the temporal lobe; and (3) fibres that terminate in the olfactory tubercle and pyriform cortex in the frontal lobe (Rosene and Heimer, 1977; Turner *et al.*, 1978). Secondary olfactory projections reach the orbitofrontal cortex directly from intracortical afferents (Krettek and Price, 1977; Potter and Nauta, 1979), and indirectly through connections of the olfactory tubercle and pyriform cortex to the mediodorsal thalamus (Heimer, 1972). In the temporal lobe, secondary olfactory projections heavily invade the amygdala and entorhinal cortex (Krettek and Price, 1977). Electrophysiological studies have identified areas in the primate orbitofrontal and temporal cortex and mediodorsal thalamus that are responsive to olfactory stimuli (Benjamin and Jackson, 1974; Tanabe *et al.*, 1975*a*, *b*; Yarita *et al.*, 1980).

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The present investigation assessed a variety of olfactory functions in a patient who had undergone extensive bilateral medial temporal lobe resection, a procedure that is believed to have eliminated both the primary and secondary olfactory areas in the temporal lobe. The purpose of this study was to measure the functional capacities of the frontal olfactory system in the absence of the pathways to the temporal lobes.

SUBJECTS

The subjects of this report are the amnesic patient, H.M., and five groups of normal subjects. All gave informed consent to participate in the investigations.

Case H.M.

H.M., a 55-year-old man, was operated upon when aged 27 years following a 16-year history of cerebral seizures that had been uncontrolled by medical treatment. The surgical resection involved bilateral removal of the amygdala, uncus and anterior two-thirds of the hippocampus and parahippocampal gyrus (Scoville *et al.*, 1953). The excision probably included most of the pyriform cortex in the uncus, but other components of the first nerve projection, specifically the olfactory tubercle and adjacent pyriform cortex on the basal surface of the frontal lobe, might have been partially or completely spared. The olfactory bulbs or tracts could have been damaged by retraction of the frontal lobes, although the patient is not anosmic. In animals, anosmia occurs only after total disruption of the primary olfactory afferents or extensive destruction of the anterior pyriform cortex (*see* Sapolsky and Eichenbaum, 1980). In H.M., retraction of the frontal lobes might also have produced damage to the orbitofrontal cortex, but he demonstrates none of the more salient clinical features of frontal lobe disease (Hécaen and Albert, 1975; Blumer and Benson, 1975).

The most obvious consequence of the operation is the patient's persistent anterograde amnesia. Numerous studies revealed a nearly complete inability to form long-term memories (Scoville and Milner, 1957; Milner *et al.*, 1968; Corkin *et al.*, 1981); notable exceptions are certain motor, perceptual and cognitive skills (Milner, 1962; Corkin, 1968; Nissen *et al.*, 1981; Cohen and Corkin, 1981). H.M.'s performance on short-term memory, perceptual, motor and cognitive tasks is essentially normal (Milner *et al.*, 1968; Wickelgren, 1968; Corkin, 1982) although his perception of the affective qualities of certain stimuli is diminished (Hebben *et al.*, 1981). Since the operation, his neurological symptoms have remained stable and include ataxia of gait and polyneuropathy; recently there was a reduction in the Wechsler IQ rating from the bright normal to the average range (Corkin *et al.*, 1981).

Normal Control Subjects

H.M.'s performance on the olfactory tests was compared to that of five normal control groups that had previously been examined or were concurrently tested with the same methods used with H.M. Different control groups were used for different tasks, depending upon the time and location of the experiments, and the availability of subjects. The five groups were (1) 3 men aged 45 to 58 years (mean age, 54.0 years) tested in detection and discrimination tasks; (2) the 10 normal control subjects from Potter and Butters' (1980) study, who had a mean age of 55 years; (3) 15 female college students, aged 18 to 20 years (mean age, 19.3 years) tested in detection tasks; (4) 2 female research assistants, aged 24 and 25 years, tested in discrimination tasks; and (5) 3 men aged 23, 48 and 55 years, tested in adaptation tasks.

OLFACTORY TESTS: METHODS AND RESULTS

In order to evaluate a wide range of olfactory perceptual functions, tests were designed to measure detection of different odours, discrimination of different intensities of the same odour, adaptation to a strong odour, and discrimination of different odours by quality. Because of H.M.'s severe amnesia, the memory component of the tasks was minimized. Cue cards were present during testing to remind him of the instructions, and no test, except the naming tasks, required him to remember a stimulus for more than a few seconds. The stimuli consisted of various common food flavourings and reagent grade chemicals used without further purification. All odours were presented to both nostrils simultaneously, using open bottles or specially constructed sniff chambers, except in the internasal adaptation test, where stimulation was unilateral.

Detection: Methods

Two tests of odour detection were administered, each based on a different psychophysical procedure. One used the method of limits and the other the method of signal detection.

Methods of limits. The stimuli for this test consisted of 10 sequential twofold water dilutions of each of four stock odorants; almond (McCormick), ethanol (180 proof), lemon (McCormick) and acetone. Each 1 ml stimulus was matched against a blank sample (distilled-deionized water) in 100 mm test-tubes. For each of the 10 odour and blank pairs, starting with the highest odour concentration, the subject was allowed one sniff each of the odour and blank samples, offered randomly in rapid succession, and then asked to identify which of the two tubes contained odorant. The intertrial interval was 30 s. Based on the assumption that an initial error in this test indicated proximity to sensitivity threshold, the threshold score for each odour was quantified as the highest dilution for which detection up to and including that dilution was errorless.

H.M. was tested four times on each odour. His mean threshold for each was compared with those of 3 age-matched male and 15 younger female normal control subjects, all of whom were tested once with each odour.

Method of signal detection. Odour-detection performance was also assessed by the signal-detection method using apparatus and procedures identical to those of Potter and Butters (1980). The stimuli were 1.3 mM n-butanol (MCB, reagent grade) in distilled-deionized water, and water alone, presented in specially constructed constant volume and vapour pressure sniff chambers (Engen *et al.*, 1975; Mair *et al.*, 1978). Single stimuli were presented successively in random order on 30 trials. On each trial the subject was allowed a single sniff and then was required to identify the stimulus as odour ('signal') or blank ('noise'). Feedback on the accuracy of the response was provided immediately and followed by a 30 s intertrial interval. A d' measure was calculated from the observed 'hit' and 'false alarm' rate probabilities (Elliot, 1964). H.M. was tested twice; his scores were compared with the results of 10 normal adults with a mean age of 55 years, who had been given the identical test (Potter and Butters, 1980).

Detection: Results

When tested using the method of limits, H.M. correctly detected dilutions of each of four odorants that were approximately as high or higher than those detected by a larger group of younger normal adults (Table 1). With the signal-detection paradigm, H.M. correctly identified a weak stimulus 75 per cent of the time; he erroneously identified the blank as a stimulus only 25 per cent of the time. His consequent d′ of 1.22 was at least as good as that of the 10 normal adults (mean d′ = 1.10) tested by Potter and Butters (1980).

TABLE 1 DETECTION OF COMMON ODORANTS MEAN DILUTION AT THRESHOLD

Subjects	*Mean age*	*Odour* *Almond*	*Ethanol*	*Lemon*	*Acetone*
Normal control					
Females (n = 15)	19.3	—	4.8	3.7	—
Males (n = 3)	54.0	5.7	3.3	2.7	5.1
H.M.		5.0	4.6	5.5	5.2

Discrimination of Intensity. Methods

Threshold for discrimination of intensity difference was tested using the same four odorant dilution series as in the first detection test. In the intensity discrimination task, however, subjects were asked to choose the stronger stimulus in 10 odour pairs, each composed of an odorant in its lowest dilution (i.e., highest concentration) and the same odorant in a higher dilution (i.e., lower concentration). On successive trials presented at 30 s intervals, the lowest dilution (strongest stimulus) was paired with the weakest and then successively stronger stimuli until, on the last of the 10 trials, the two samples were identical. Threshold for intensity difference discrimination was defined as the lowest dilution sample for which identification up to and including that dilution was errorless. H.M. was tested twice with each of the four odorants; his scores were compared with those of 3 age-matched normal control subjects.

Discrimination of Intensity: Results

H.M.'s capacity to distinguish odour intensities is also normal. For each of the four common odorants, H.M. could successfully discriminate among odours of the higher concentrations used (Table 2).

TABLE 2 INTENSITY DIFFERENCE THRESHOLD FOR COMMON ODORANTS MEAN DILUTION AT THRESHOLD

Subjects	*Mean age*	*Odour* *Almond*	*Ethanol*	*Lemon*	*Acetone*
Normal control					
Males (n = 3)	54.0	8.2	8.3	7.3	1.3
H.M.		2.0	6.5	6.5	2.0

Adaptation: Methods

Using the same apparatus and signal detection-with-feedback procedure as described for the intensity-discrimination test, H.M. was tested on detection of 10 mM aqueous *n*-butanol (MCB in pH 7 buffer and 1.3 mM *β*-phenethyl alcohol (Aldrich Gold Label) in pH 7 buffer during adaptation to the same odour, to the other odour, or to a blank pH 7 buffer diluent presented in equilibrium sniff chambers (*see* Method of signal detection, *above*). On each adaptation test, he first sniffed continuously for 100 s either the blank or a strong solution of *n*-butanol (500 mM) or of *β*-phenethyl alcohol (17 mM) in open 250 ml Erlenmeyer flasks. Then he sniffed a sample either of one of the test odorants or of the blank and stated whether a smell was present. During the subsequent 10 s intertrial interval, he sniffed the adapting stimulus. The 6 combinations generated from the 3 adapting and 2 test odorants were each presented in 40 trial blocks. In order to allow sufficient time for equilibration of odour concentration in the sniff chambers, each stimulus was contained in four chambers, which were used in rotation. The entire series of tests was administered to H.M. twice. On separate days, he was tested in the control (blank 'adapting' stimulus), adaptation and cross-adaptation conditions with only one test odour, and the order of conditons was varied (*see* Table 3 *below*). Each condition with *n*-butanol as the test stimulus was administered to two normal male subjects on one day.

Internasal adaptation was also investigated. H.M. and a normal male subject aged 55 years were adapted unilaterally to 50 mM *n*-butanol by covering the left nostril with the right thumb and sniffing with the right nostril for 10 s. Immediately following, the subject covered his right nostril with his left thumb and sniffed with his left nostril either 10 mM *n*-butanol or a blank.

Adaptation: Results

Prior adaptation to a stong intensity of the stimulus odorant decreased H.M.'s ability to detect odours in the normal way (Table 3). He demonstrated significant detection of *n*-butanol and *β*-phenethyl alcohol when the 'adapting stimulus' was only the buffered diluent water. When the adapting stimulus was a stronger concentration of the test odour, detection fell to chance for both stimuli. In the

TABLE 3. ADAPTATION AND CROSS-ADAPTATION d′ FOR CASE H M.

Condition	*Order of conditions*[a]	*Adapting stimulus*	*Test stimulus*[b]	*Hits/ false alarms*	*d′*	*P value*[c]
Control	1	Blank	BuOH	17/5	1.72	< 0.001
	2	Blank	BuOH	15/5	1.20	0.003
Adaptation	1	BuOH	BuOH	6/8	−0.27	0.318
	2	BuOH	BuOH	8/6	0.27	0.318
Cross-adaptation	1	PeOH	BuOH	16/5	1.52	< 0.001
	2	PeOH	BuOH	20/15	0.96	0.077
Control	3	Blank	PeOH	10/2	1.41	0.003
	2	Blank	PeOH	13/8	0.38	0.215
Adaptation	3	PeOH	PeOH	9/9	0.00	0.563
	2	PeOH	PeOH	10/9	0.13	0.437
Cross-adaptation	3	BuOH	PeOH	10/2	1.04	0.019
	2	BuOH	PeOH	11/8	0.64	0.077

[a] 1. Control, then adaptation, then cross-adaptation. 2. Cross-adaptation, then control, then adaptation. 3. Control, then cross-adaptation, then adaptation. [b] BuOH = *n*-butanol; PeOH = *β*-phenethyl alcohol. [c] Exact probability calculated from Bernoulli Trials (Apostol, 1962).

cross-adaptation paradigm, where the adapting stimulus was a strong odour that differed in quality from the test odour, H.M.'s detection of the test odour was well above chance, though lower than when the 'adapting stimulus' was water. While overall performance varied in different test sessions, variations in the order of control, adaptation and cross-adaptation conditions had no effect on relative scores for the three conditions. When the combined adaptation scores for the two sessions were compared to the combined scores for the control conditions, H.M.'s correct answers were lowered after adaptation by 3.10 and 5.52 standard deviations for β-phenethyl alcohol and *n*-butanol, respectively. His combined correct answers after cross-adaptation were lowered by only 0.95 and 1.31 standard deviations, respectively. By comparison, when two normal male subjects, aged 23 and 48 years, were adapted to *n*-butanol (80 trials each), their number of correct answers was lowered by 11.0 and 5.0 standard deviations, respectively. In contrast, cross adaptation to β-phenethyl alcohol did not affect detection in one control subject and reduced the performance of the other control subject by only 1.4 standard deviations.

In the internasal adaptation condition, the single normal control subject lost sensitivity (Table 4). Similarly, H.M. significantly detected *n*-butanol unilaterally before adaptation, but his performance fell to near chance after internasal adaptation. The difficulty of maintaining patency of both nostrils during this procedure precluded the running of a more complete series of experiments. H.M.'s contralateral adaptation was not as profound as that of the normal control subject, nor as his own bilateral adaptation (Table 3). Moreover, in a separate experiment (Table 4), when the initial 100 s adapting sniff was omitted, bilateral adaptation was less profound than when it was given. Although H.M.'s performance using his left nostril alone did not differ significantly between nonadapted and adapted conditions ($P = 0.12$), there is no evidence to suggest that he did not experience contralateral adaptation.

TABLE 4. INTERNASAL ADAPTATION: d′ FOR DETECTION OF *n*-BUTANOL

Subject	*Adaptation condition*	*Adapting stimulus*	*Hits/ false alarms*[a]	*d′*	*P value*[b]
Normal control (n = 1, aged 55 yrs)	Control	Blank	16/5	1.52	0.001
	Adaptation	BuOH[c]	5/2	0.60	0.215
H.M.	Control	Blank	9/2	1.15	0.019
	Adaptation	BuOH	8/5	0.42	0.215
	Control (bilateral)	Blank	14/6	1.05	0.008
	Control (bilateral)	BuOH	11/6	0.66	0.077

[a] Out of 20 possible for each. [b] Exact probability calculated from Bernoulli trials (Apostol, 1962). [c] BuOH = *n*-butanol.

Discrimination of Odour Quality: Methods

H.M.'s ability to discriminate odours was measured with three tests that differed both in the mode of stimulus presentation and in response requirements.

Method of signal-detection. One technique was based on the signal-detection method. The stimuli, apparatus and procedure were identical to that used by Potter and Butters (1980). On each of 32 trials, a pair of suprathreshold stimuli were presented in succession with a 15 s silent interval separating the two presentations. On half of the trials, the two stimuli were different, the condition defined as the 'signal'; on the other half of the trials, they were identical, the condition defined as the 'noise'. After presentation of the stimulus pair, the subject was asked whether the odours were the same or different. Each trial was followed by a 30 s intertrial interval. Discrimination was tested with three odour pairs: methylsalicylate *versus* guaiacol (easiest for normal control subjects to discriminate), eugenol *versus* guaiacol and allyl caproate *versus* amyl proprionate (most difficult for normal control subjects to discriminate). For each odour pair d′ was determined by relating H.M.'s correct identifications of different stimuli to incorrect identifications of the same stimuli as being different. His d′ scores were compared to the scores of 10 normal adults as reported by Potter and Butters (1980).

Triangle match-to-sample-test. This test involved a matching-to-sample procedure in which the subject was asked to match a weak sample odour to one of two choices, either a stimulus of identical quality and the same or stronger intensity, or a distractor that differed from a sample in quality and from the other match stimulus in both quality and strength. The subject was instructed to match the sample by odour and not by strength. On half of the trials, the sample and the correct match stimulus were the same both in quality and intensity, whereas on the other half the sample and the correct match were the same in quality but not in intensity. The stimuli included 1.7 mM (weak) and 8.3 mM (strong) β-phenethyl alcohol and 10 mM (weak) and 50 mM (strong) *n*-butanol all diluted in pH 7 buffer and presented in open 250 ml Erlenmeyer flasks. During each of the two testing sessions, H.M. was given 10 trials with each of the four sample and match combinations, the presentation order of sample and match stimuli was randomized. On each trial, a 5 to 10 s sniffing of the sample was followed immediately by a 5 to 10 s sniffing of each match stimulus.

Matching and naming of common odours. In this task, the subject was asked to match a sample odour stimulus or blank (distilled-deionized water) to one of 9 common odours or a blank each presented in a 3 ounce brown bottle. The odours were coconut (McCormick), mint and peppermint (McCormick), almond (McCormick), vanilla (McCormick), orange (McCormick), cloves (McCormick), raspberry aldehyde (Givaudan) and β-phenethyl alcohol ('rose,' Eastman). On each of 10 trials involving a different sample odour, the subject was given the sample and 10 potential match stimuli, and instructed to sniff each bottle and find the one that contained the same odour as the sample. Repeated sniffing of sample and match stimuli was allowed. After the match choice was made, the subject was asked to identify the stimulus by name or, if no name was given, to make a verbal association. H.M.'s percentage of correct responses for matching and naming on two completions of the test was compared to those of 3 age-matched normal males and 2 younger adults.

Two modifications of this procedure were also administered. In one, H.M. was asked to match a sample to one of only two match stimuli. He performed this task three times with each of the 10 sample stimuli. In a recognition version of the task, H.M. and a normal male subject were presented in successive trials with one of the 10 sample stimuli and asked to identify the name of the odour from a written list of five odour labels. In the 10 lists, the labels of the 10 sample stimuli occurred with equal frequency.

As a control for modality of stimulus presentation, H.M. was asked to name four common foods separately by odour, touch, and sight. Thus, in separate presentations, he tried to identify orange, onion, lemon and banana, under three conditions: (1) when allowed only to sniff the crushed food, (2) when allowed only to handle the food in an opaque paper bag, and (3) when allowed only to see the food.

Discrimination of Odour Quality: Results

In contrast to a normal capacity to detect odours, make intensity discriminations and adapt to odours, H.M. demonstrated no ability to discriminate the quality of odours. In the signal-detection testing of quality discrimination, H.M. could not reliably identify a pair of different odours as different, even when the odour pair was one that normal control subjects found easy to differentiate (Table 5).

TABLE 5 ODOUR-QUALITY DISCRIMINATION: MEAN d′

Subjects	*Mean age*	*Amyl proprionate vs. allyl caproate*	*Eugenol vs. guaiacol*	*Guaiacol vs. methyl salicylate*
Normal control (n = 10)[a]	55.0	1 8	2.4	3.3
Case H.M.		0.0 (14/14)[b]	0.5 (14/12)	0.0 (14/14)

[a] From Potter and Butters (1980). [b] (Hits/False alarms) out of 16 possible for each.

In the triangle match-to-sample test, H.M. could not reliably match an odour stimulus to an identical quality-matched stimulus or to an odour of a different quality and strength. Although he could match a weak β-phenethyl alcohol sample perfectly to the same stimulus paired with strong *n*-butanol, he scored at chance in matching that sample to strong β-phenethyl alcohol paired with *n*-butanol. H.M. scored at chance on both tasks where he was required to match a weak *n*-butanol sample (Table 6).

TABLE 6 ODOUR-QUALITY DISCRIMINATION. H.M 'S PERFORMANCE ON TRIANGLE MATCH-TO-SAMPLE TEST

Sample stimulus	*Match stimuli*[a]		*Mean percentage correct*
	Strong	*Weak*	
Weak PeOH	BuOH	PeOH	100
Weak PeOH	PeOH	BuOH	50
Weak BuOH	PeOH	BuOH	55
Weak BuOH	BuOH	PeOH	50

[a] BuOH = *n*-butanol; PeOH = β-phenethyl alcohol.

On the common odour-matching task, normal control subjects score between 85 and 95 per cent correct. In contrast, H.M. performed at chance level (11 per cent correct). On each of two repetitions of the test he correctly matched only one of 9 odour samples to a test odorant. He always correctly identified the blank sample and match stimuli. Even when the number of match stimuli was reduced

TABLE 7. ODOUR-QUALITY DISCRIMINATION: MEAN PERCENTAGE CORRECT ON COMMON-ODOUR MATCHING[a]

Subjects	*Mean age*	*Matching*	*Naming*
Normal control			
10 choice			
Females (n = 2)	24.5	95.0	85.0
Males (n = 3)	54.0	85.0	90.0
H.M.			
10 choice		11.0	5.6
2 choice		53.0	—

[a] Excludes trials with the blank stimulus.

to two, his score remained at chance (50 per cent) (Table 7). Normal subjects, when asked to identify these common odours, could name 85 to 95 per cent correctly, but H.M. consistently identified only the nonodorous water stimulus. He did use odour labels (for example, 'flowers', 'decaying matter', etc.) but the names bore no obvious relationship to the actual odour qualities and were not consistently applied (Table 8). H.M. sometimes repeated the same name for different odours presented in sequence but when asked if these odours smelled alike would insist not, and offered additional descriptors to clarify the differences. In two repetitions of the recognition version of the task, H.M. again identified the blank sample, but correctly identified the name of the sample only twice, resulting in a performance score no better than chance. The normal control subject correctly recognized the name of each odorant.

When asked to name four common foods by odour, H.M. failed in each case, again applying odour labels inconsistently. Yet he could easily name each food when handling it in a bag or upon brief visual examination.

TABLE 8 NAMING OF COMMON ODORANTS BY H M

Odour	*Test 1*	*Test 2*
Coconut	'Soap'	'Flowers'
Mint	'Flowers'	'An acid'
Almond	'A wild flower'	'An acid'
Lemon	'Flowers'	'An acid'
Vanilla	'Weak roses'	'Newly made paper'
Orange	'An acid'	'Weak perfume'
Cloves	'Fresh woodwork'	'Dead fish, washed ashore'
Raspberry	'Flowers'	'Carrion, a squirrel'
Rose	'A rose flower'	'Bad water'
Water	'I can't smell anything'	'I can't smell anything'

DISCUSSION

H.M.'s test performance demonstrates a striking dissociation of olfactory perceptual capacities. His performance on the intensity dimension is preserved, whereas his performance on the quality dimension is severely compromised. On the intensity dimension, he has a normal capacity for detection of weak odorants, for differentiation of odours by concentration, and for normal adaptation to a strong odour.

The present results show that odour quality discrimination and recognition are not necessary for detection, adaptation or intensity discrimination. Indeed, H.M. could sometimes use the intensity dimension to perform well in odour-quality matching tasks. He always matched the blank sample correctly in the common odour matching-to-sample task, and under one condition in the triangle test, H.M. could distinguish a strong *n*-butanol solution from weak β-phenethyl alcohol. In striking contrast, his performance on this task was consistently at chance when forced to match by odour quality when the intensities of sample and match stimuli were comparable. Other tests also revealed that H.M. is unable to differentiate or recognize odours by quality, whether tested by same-different judgements, matching, or naming. H.M. easily identified by touch or sight the same common foods that he could not name by odour.

Even though H.M.'s olfactory deficit is modality specific, it should not be termed an agnosia (Teuber, 1965; Corkin, 1978). His impairment involves not only a loss of the appreciation for the meaning of stimuli but also includes elementary functions, such as same-different judgements: H.M. is not only without the ability to recognize odours, he cannot identify different odours as different or identical odours as the same. His pattern of abilities and deficits clearly and consistently indicates that the perceptual phenomena of detection and discrimination are dissociable by cerebral damage.

H.M.'s odour discrimination impairment is not attributable to his well-documented memory deficit. Although the 15 s interstimulus interval in the method of signal detection might have increased the difficulty of the task for H.M., he was also impaired on two other tests of odour quality, the triangle match-to-sample test and common odour matching, in which the memory component was minimal. Moreover, during numerous experiments, H.M. has consistently demonstrated a normal ability to hold and use information in immediate or short-term memory (Corkin *et al.*, 1981). None of the tests used in this study, with the exception of odour and object naming, required the use of information outside his intact, immediate memory. For example, in the common odour matching task, H.M. often sniffed the sample odour only once prior to sequentially sniffing each of the 10 potential match stimuli. Then, with confidence, he would select a match, for example, from the middle of the array. When asked to check his choice by again sniffing the sample and chosen match stimulus, he invariably confirmed his choice, which was correct only by chance; it appeared that H.M. could remember which match had been positive while testing others, regardless of its location in the array. Not even his poor performance at odour naming is explained by the global anterograde amnesia. All the odours used were items of common experience to people in childhood, and H.M.'s memory for details from that period of his life is normal. His performance was not improved when odour names were given. It is also unlikely that his inability to name common odours is due to retrograde amnesia because the deficit is specific to the olfactory mode. He easily names by sight or touch the same objects he cannot identify by smell. Once, having correctly identified a lemon by sight, he sniffed it and remarked, 'Funny, it doesn't smell like a lemon!'

Impairment of olfactory abilities is also seen after left or right unilateral temporal lobectomies that include the same olfactory and subcortical structures removed in H.M. Rausch *et al.* (1977) found deficits on a delayed matching-to-sample task; Eskenazi *et al.* (1981) described poor performance on various tests of odour discrimination, including matching, differentiation, identification and delayed recognition memory. Comparing the magnitude of these deficits to H.M. suggests that he is more severely impaired in odour quality discrimination, perhaps because olfactory structures were removed bilaterally in his case. H.M.'s deficit in odour recognition is also greater than that of patients with unilateral or bilateral amygdalotomy, who demonstrate mild and transient deficits in odour naming (Hughes and Andy, 1979). Unlike some patients with unilateral temporal lobe lesions (Rausch and Serafetinides, 1975), frontal lobe lesions (Potter and Butters, 1980), or Korsakoff's disease (Jones *et al.*, 1978), H.M. is not impaired in the ability to detect the presence of an odour.

Considering that H.M. had undergone a supraorbital craniotomy and bilateral retraction of the frontal lobes, the residual olfactory capacity was impressive. Yet his normal capacity for detection indicates that the olfactory bulbs and tracts must be at least partially intact. Furthermore, the limits of the estimated damage allow for a partially intact secondary olfactory route from the olfactory tubercle and adjacent cortex to the orbitofrontal olfactory neocortex, both by way of the mediodorsal thalamus and by intracortical connections. The medial temporal lobe resection probably did eliminate a substantial portion of the afferents to the olfactory frontal cortex and thalamus. Apparently the remaining inputs from the olfactory tubercle and cortex are insufficient to support odour discrimination, but are adequate to allow odour detection. The strength and selectivity of the olfactory deficits revealed in H.M. suggest a critical role for medial temporal lobe structures in the perception of odour quality. Taking these results together with previous findings of deficits in odour discrimination after damage to connections between the mediodorsal thalamus and the frontal cortex in man and animals, it may be concluded that an intact temporal olfactory pathway is not sufficient to support olfactory perceptual functions. Apparently both divisions of the higher olfactory pathways are necessary for the discrimination and identification of odours. The most striking aspect of H.M.'s performance, a complete dissociation between detection and discrimination, may be uniquely related to involvement of medial temporal lobe structures bilaterally.

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VISUAL RECEPTIVE FIELDS AND RESPONSE PROPERTIES OF NEURONS IN HUMAN TEMPORAL LOBE AND VISUAL PATHWAYS

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SUMMARY

Recordings were made from depth electrodes placed in medial temporal and occipital lobes for the localization of seizure foci in patients with medically intractable psychomotor epilepsy. Electrodes were located in the amygdala and at three rostrocaudal levels of the hippocampal formation including the posterior hippocampal gyrus, which lies medial to the portion of the geniculostriate pathway which passes through the temporal lobe.

1. Approximately 10 per cent of single units recorded from microelectrodes chronically implanted in medial temporal sites were visually responsive. Some of the units in the posterior hippocampal gyrus displayed receptive field characteristics similar to those reported in lower primates, including circular or linear shape, monocular or binocular response, variable (1 to 10 deg) receptive field size, retinotopic organization and sustained or transient response.
2. Visually responsive units were also recorded from lateral geniculate nucleus, pulvinar nucleus and occipital cortex, and their basic response form and latencies compared with the short latency visually responsive cells in medial temporal lobe.
3. The heterogeneity of receptive field characteristics in the medial temporal lobe is consistent with the existence of more than one visual input to this region, while their retinotopic relationship differentiates these receptive fields from those of units studied in the inferior temporal lobe of lower primates.
4. Properties of visual pathways in this region are discussed in relation to several types of temporal lobe function and to memory.

Recordings from these neurons offer a rare opportunity for comparison of central visual response properties and receptive field characteristics of humans with those reported in animal studies.

INTRODUCTION

Most information on neural mechanisms of vision has been derived from neurophysiological animal studies, and comparable information is difficult to obtain regarding the human visual system. Although scalp recordings have been useful in providing information about structural and functional aspects of the human visual system (*see* Allison *et al.*, 1977; Blumhardt and Halliday, 1979; Jeffreys, 1977; Maffei and Campbell, 1970; Spekreijse *et al.*, 1977), single cell recordings are lacking for direct comparison with the considerably greater volume of data from animals, data which form the basis for existing knowledge of the neural coding of visual information (*see* Bishop *et al.*, 1972; Hubel and Wiesel, 1977; Kuffler, 1953). A single exception is the work of Marg and coworkers (Marg *et al.*, 1968; Marg and Adams, 1970; Marg, 1973), who mapped several receptive fields of cells recorded in human occipital cortex. To our knowledge, no other single unit receptive field mapping of visually responsive cells has been reported in the human visual system.

It has long been known that the optic radiations, as they project from thalamus to visual cortex, are divided into two separate contingents of fibres (Meyer, 1907). Optic radiation fibres representing the upper half of the retina project directly back to the occipital lobe, whereas fibres representing the lower retina are deflected laterally into the temporal lobe before turning in a caudal direction and continuing to the occipital area (Cushing, 1922). As the lateral fibre contingent moves caudally in the temporal lobe, a portion of it passes through the core of the parahippocampal gyrus (Polyak, 1957). Evidence for considerable variability in the distribution of these visual fibres in the temporal lobe is provided by variation in the size of visual field defects resulting from standard anterior temporal lobectomy for relief of complex partial seizures, and by the amplitude of visual evoked potentials recorded in the posterior parahippocampal gyrus (Babb *et al.*, 1982). In those patients where optic radiation fibres course more medially in the temporal lobe, the potential exists for recording units representing thalamic visual input to and/or through this region. The receptive field data which are the nucleus of this report, are considered to be the result of just such a mesiotemporal trajectory.

In the present study, single and multiple unit activity was recorded from electrodes placed in the medial temporal lobe to obtain diagnostic information used in the surgical treatment of patients suffering from medically intractable temporal lobe epilepsy. Diagnostic information is increased when localization of the site of seizure onset is obtained from depth electrodes placed stereotaxically in medial temporal lobe structures (Crandall, 1973, 1975). The additional use of platinum microwire electrodes capable of resolving single unit activity adds to the diagnostic utility of such recordings (Babb and Crandall, 1976; Babb *et al.*, 1981). Recordings of single cell response to visual stimuli were carried out with the informed consent of the patients at times during their stay in hospital when they were unoccupied by any specific clinical requirements. Concurrent depth telemetry of macroelectrode placements allowed testing of visual response at microelectrodes without interruption of monitoring for ictal activity so that over the course of these studies, clinical needs of patients always took precedence over visual testing.

The receptive field maps of the cells reported here are taken from a larger study which screened the sensory responsiveness of over 300 medial temporal lobe units recorded in 23 patients from the Clinical Neurophysiology Program (CNP) at the University of California Los Angeles (UCLA). The basic visual response properties and stereotaxic localization of these units is described in order to illustrate the extent to which the visual system is represented in this region. Basic response properties of several cells recorded in the visual thalamus and in the occipital lobe are also reported in order to compare their response characteristics with medial temporal lobe neurons.

The units described in the present report represent the only subcortical and temporal lobe visual neurons which have been recorded from the human brain. As such, these data allow comparison of human visual response characteristics with those of the lower primate visual system. The results indicate a relative absence of direct visual input to the amygdala and anterior hippocampal formation, whereas the posterior parahippocampal gyrus contains many cells which are visually responsive. Because it lies adjacent to the optic radiations and in proximity to the circumstriate and visual association cortices, the human posterior parahippocampal gyrus is in an anatomically favourable position for receiving convergent visual inputs. Moreover, the variations in the types of receptive fields we encountered are consistent with the conclusion that this region is a site of convergence of several visual pathways.

METHODS

Subjects

Data for this report came from 23 patients in whom medial temporal lobe neurons were tested for visual response. During a previous admission to hospital of each patient, 24-h surface EEG telemetry and video recordings of spontaneous ictal behaviour had verified the likelihood of focal complex partial seizures, but had failed to provide sufficient localization of the site of onset to indicate operation. In order to provide this information, chronic bilateral depth electrodes were aimed at the basolateral amygdala as well as sites at two or three anterior to posterior levels within both pes hippocampi and parahippocampal gyri (also termed hippocampal gyrus). All patients received a screening test for visual response to full-field light stimuli of varying durations. From this test, data were obtained describing the proportion of visually responsive units and their location in the temporal lobe. In addition, unit recordings were obtained from thalamic sites in 3 patients, from the occipital lobe in 1 patient, and receptive fields of medial temporal units were mapped in 1 patient. Patient characteristics and visual system data obtained during neurological examination of these 5 patients are shown in Table 1. Except as noted in Table 1, all these patients showed normal visual acuity, full visual fields, clear fundi, normal pupillary reactions, normal accommodation and normal extraocular motor control. .Side of seizure origin is included in Table 1 to allow evaluation of any influences of epileptiform activity upon visual response. For example, the receptive field mapping in Case 127 was carried out on the side contralateral to seizure onsets, while occipital lobe unit responses in Case 122 were ipsilateral to the epileptic focus. Ictal activity was never observed in thalamic sites.

Electrodes and Recording

Patients were tested three to six days after surgical implantation of 0.8 mm diameter stainless steel cannula electrodes through which 40 μm diameter platinum alloy microwires were extended another 5.0 mm. Cannula electrodes were insulated to within 1.0 mm of the tip; microwires were insulated except for the 40 μm diameter end surface exposed when they were cut to length. Tips of the microwires were localized during implantation using ventriculograms which allowed visualization of the outline of limbic structures and comparison with the stereotaxic atlas of Talairach *et al.* (1967). Postoperatively, a more exact localization of electrode tips measured from x-rays was determined by plotting their

TABLE 1 CHARACTERISTICS OF PATIENTS

Patient	*Sex*	*Age (yrs)*	*Seizure origin*	*Anticonvulsants*	*Data from neurological examination relevant to vision*
63	M	28	Right temporal	Phenytoin Phenobarbitone	Moderate nystagmus on lat. gaze bidirectionally, possibly secondary to phenytoin
65	F	34	Right temporal lobe	Phenytoin Primidone	Diabetic from childhood but no visual symptoms or complications
72	M	25	Bilat temporal lobe	Phenytoin Phenobarbitone Primidone	Bilat. pendular nystagmus from early childhood. R. eye: foveal and nasal vision absent due to retinal degeneration; able to count fingers in temporal field. L. eye: full visual field, Jaeger acuity J-11 at standard distance but J-1 with card held close to eye.
122	F	20	Right occipital lobe	Carbamazepine	R. occipital cyst at borders of Brodmann areas 37 and 19. Epileptic discharge accompanied by moving coloured phosphenes. No visual field defect or scotoma detectable with perimetry; interictal vision normal.
127	F	21	Left temporal lobe	Carbamazepine	Myopia corrected with contact lenses. Slight dysconjugate gaze on lat abduction.

position on coronal sections from the atlas of Talairach which had been enlarged 5 times. Using this technique, electrodes which had not reached their intended target were excluded from analysis within the population of cells recorded in a specific site. Histological analysis of electrode tracks located in excized anterior temporal lobe specimens in a previous study (Halgren *et al.*, 1978*b*) showed that accurate placement was achieved if the surgical goal was limited to stereotaxic positioning of electrode tips within a target structure. Although the accuracy of stereotaxic surgery is not sufficient to pin-point electrode tips to specific cortical laminae, or small subnuclear divisions, nevertheless because the hippocampus forms the floor and medial wall of the inferior horn of the lateral ventricle, stereotaxic placement based upon a radiographic procedure in which the ventricle itself is outlined allows a substantially greater degree of accuracy than is possible using bony structures as landmarks.

Activity from microwires referred to Cz was amplified conventionally *via* FETs over a bandpass of 0.3 Hz to 5 kHz and recorded on magnetic tape for later point process computer analysis. Details of electrode construction, recording and analysis procedures are reported in Babb *et al.* (1973) and Babb and Crandall (1976). Unit activity recorded from the 40 μm wires was often the combined activity of several units. When sufficient spike height differences allowed, window discriminators were used to separate the activity of two units recorded by the same electrode. Only single cell activity was used when receptive fields were plotted.

Visual Testing

Visual stimuli were presented in a darkened, shielded recording chamber with ambient illumination in the low mesopic range (0.1 cd/m^2). This is the luminance level referred to as 'background' throughout the report. In the screening tests for the group of 23 patients, two types of visual stimuli were used. Trains of at least 100 brief diffuse flashes from a Grass photostimulator (× 4 intensity) were presented at a rate of 0.5 Hz. The second test used full field luminance increments 2.7 log units above background of 1.0 to 5.0 s duration. Poststimulus time histograms (PSTHs) were constructed during off-line analysis in order to detect responsive neurons. For the visual receptive field mapping, a variety of visual stimuli were employed, including brief diffuse flash, and increments or decrements in full-field luminosity of 2 to 30 s duration. Also, for receptive field mapping, a hand- or tripod-held projector was used to display a variety of slits, bars and spots of different sizes and contrasts. Visual stimuli were presented on a 70 × 70 deg tangent projection screen 1.14 m from the subject's eyes. During presentation of stimuli, subjects were instructed to maintain gaze on a light emitting diode (LED) in the centre of the tangent screen and during some tests, to report changes which consisted of dimming the 3.4 cd/m^2 red LED by 0.5 log unit. Thus, attention to the fixation point could be maintained and assessed while stability of fixation was measured by recordings from capacity-coupled disc electrodes attached to the outer canthi and above and below the right eye (Wurtz, 1969). This procedure allowed rejection of data in which the eyes were moving, or during obicularis oculi contraction. Head movement was minimized by positioning the occiput in a circular head rest. Electro-oculograms (EOG) of patients proved them competent at maintaining steady gaze for 10 to 30 s periods. Receptive field mapping was guided by auditory feedback of the amplified action potentials through a loudspeaker. Determination of the absolute position of the receptive field was dependent upon repetition of visual stimulus presentation until the location of the field was reliably defined. Studies of response properties of cells were sometimes only partially completed since the same medical necessities which required depth electrode placement in these patients took precedence over experimental goals.

RESULTS

The results consist of (1) a brief summary of the response statistics obtained in the visual unit screening tests along with a description of the anatomical loci of the visually responsive units and their sustained or transient response properties; (2) a detailed description of the cells from which visual receptive fields were mapped; and (3) a description of visually responsive cells recorded in the thalamus and occipital lobe.

Radiographic Localization of Visually Responsive Units

Medial temporal lobe units. The number of units recorded from all medial temporal lobe microelectrode sites in the 23 patients included in this report totalled 340. All cells were tested for response to brief diffuse flash, and on the basis of PSTH evaluation it was found that just over 10 per cent were visually responsive ($n = 35$). These responsive units were recorded from microwire bundles localized by ventriculography, and by anteroposterior and lateral radiographs as being within the following structures: parahippocampal gyrus ($n = 20$), pes hippocampi ($n = 6$) and subiculum ($n = 9$).

All electrode sites from which the above units were recorded are plotted in fig. 1 on a coronal section at the level of the posterior hippocampal formation. Each site represents the tips of a bundle of 9 microwires. Between 1 and 7 units are represented by each point, with an average of 2.3 units at the 16 sites plotted. One of the 11 parahippocampal gyrus responsive sites was located at a more rostral level but is plotted on this posterior coronal plane for ease of presentation. The same is true of the 3 subicular sites marked by filled circles. Therefore, 12 of 16 sites containing visually responsive units and 26 of the 35 responsive units were located in the posterior part of the hippocampal formation. Nearly 75 per cent of the 35 responsive neurons were located in the posterior structures even though the proportion of the 340 units tested was approximately equal between the posterior hippocampal formation (n = 120), the anterior hippocampal formation (n = 110), and the amygdala (n = 110). None of the amygdala units was visually responsive.

Filled circles represent sites at which all unit responses were transient, while triangles represent at least one sustained response at each site. Transient responses consisted of brief changes in neural discharge at the onset and/or offset of square wave shifts in luminance of 2 to 5 s duration. Sustained responses were defined as changes in firing rate extending over at least half the 2 to 5 s duration of the luminance change (*see* fig. 5). Out of the 35 visually responsive units tested, 8 of 20 parahippocampal gyrus, 1 of 9 subicular and 0 of 6 hippocampal units displayed sustained responses. Of the 9 sustained response units, an increase in luminance elicited excitatory responses from 6 units and inhibitory responses from 3 units. Mean latency of 9 sustained responses was 54.9 ms (range, 30 to 125 ms, SD, 34.5) and mean latency for 26 transient responses was 77.9 ms (range, 30 to 200 ms, SD, 51.5).

Thalamic and occipital lobe units. The pulvinar nucleus recordings were obtained from 2 patients (Cases 63 and 65) in whom microwire tips were localized in the inferior pulvinar, medial to their posterior pes hippocampi target. Lateral geniculate unit recordings were obtained in a single patient (Case 72) in whom

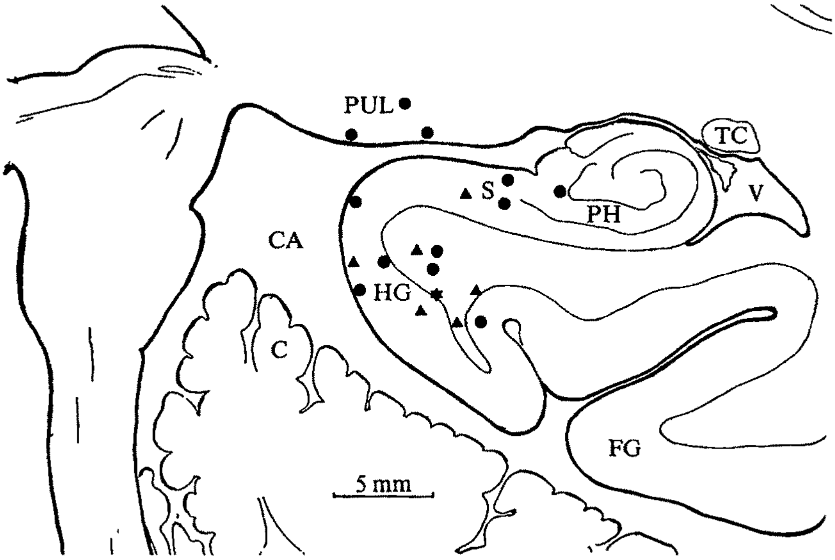

FIG. 1. Loci of electrodes recording visually responsive unit activity plotted on a coronal section at the level of the posterior hippocampal formation. Diagram derived from Talairach *et al.* (1967), ▲ = transient visual responses, ● = sustained visual responses, ★ = units with receptive field mapping. Units recorded from sites in the pulvinar were not tested for sustained response C = cerebellum, CA = ambiens cistern, FG = fusiform gyrus, HG = hippocampal gyrus, PH = pes hippocampi, PUL = pulvinar nucleus, S = subiculum, TC = tail of caudate, V = inferior horn of lateral ventricle.

microwire tips extended mediodorsally beyond the middle level of the pes hippocampi to the lateral thalamus. These are the only cases of microwire placements reaching thalamic structures in the UCLA CNP series of 150 depth implant patients, so that these sites were easily differentiated from standard placements in medial temporal lobe. In contrast to the pes hippocampal electrodes reaching thalamus in these 3 cases, no hippocampal gyrus electrodes did so. Fig. 1 shows that the hippocampal gyrus lies ventral to the pes hippocampi, so that if electrodes extend too medially, they would enter the ambiens cistern (CA). The 3 thalamic sites are plotted in fig. 1 as filled circles in the pulvinar nucleus. The two most medial sites were located in the pulvinar at this anteroposterior level. Four units were recorded from 4 electrodes at these 2 sites, and 2 of the 4 units were visually responsive. The most lateral site represents a lateral geniculate nucleus placement which was located approximately 1.5 cm anterior to this coronal section. Four units were recorded from 3 electrodes at this single site. Two of the 4 units were visually responsive. Occipital lobe recordings were obtained from microwire tips localized in and surrounding the dorsal bank of the calcarine sulcus at the anterior borders of Brodmann's area 18 and 19 and the posterior border of area 31 (Case 122).

All posterior hippocampal gyrus recordings were from placements clearly localized within the intended structure, including Case 127, from whom receptive field data were obtained for 6 cells. Response data from thalamic and occipital units will be presented later in this section.

Receptive Field Characteristics of Units Recorded in Posterior Hippocampal Gyrus

Cells for which receptive field information was obtained were recorded from an electrode bundle in the right posterior hippocampal gyrus of Case 127 indicated by a star in fig. 1. Two receptive fields will be described in detail, those of units RPG 10C and RPG 10E, which were each recorded from over a period of several hours. A third unit, RPG 10J, was studied only briefly but enough was learned about its receptive field to enable a comparison to be made between it and the other 2 units on the basis of a number of different receptive field characteristics. The summary of response features presented in Table 2 indicate that the 3 units displayed marked differences in receptive fields although visuotopically they were located together in the upper left quadrant of the visual field. Variables 1 to 12 of Table 2 subsume the data presented in the Results section, and provide an outline of the measures obtained during receptive field mapping studies. Variables 13 and 14 do not represent data but concern speculations developed in the Discussion section. It is evident from Table 2 that unit RPG 10C (which first will be described below) is representative of a comparatively higher order visual response type. Unit RPG 10E, on the other hand, displays response features more characteristic of lateral geniculate than cortical neurons. The third unit, RPG 10J, might be more closely comparable to striate cortex neurons because of its linear receptive field.

TABLE 2 CHARACTERISTICS OF POSTERIOR HIPPOCAMPAL GYRUS VISUAL RECEPTIVE FIELDS

	Variable	*RPG 10C*	*RPG 10E*	*RPG 10J*
1	Location	L. upper quadrant 30 deg eccentricity	L. upper quadrant 40 deg eccentricity	L. upper quadrant 10 deg eccentricity
2	Size	10 × 10 deg	1 × 1 deg	1 × 10 deg
3	Shape	Roughly circular	Circular	Linear
4	Orientation	None	None	Horizontal
5	Firing rate	Slow	Fast	Unknown
6	Ocularity	Binocular	Monocular	Binocular
7	Movement sensitivity	No	No	Yes
8	Surround antagonism	Yes	Possibly	Unknown
9	Information coded	Edges pattern, position?	Intensity	Edges
10	Sustained response	Yes	Yes	No
11	Complex trigger features	Yes	No	No
12	Habituation	Partial	No	Unknown
13	Cell type resembling	Nonstriate temporal lobe	Lat. geniculate or circularly symmetric cortical	Complex cell
14	Possible origin of inputs	Visual association cortex (e.g., 19 or 20)	Lat. geniculate nucleus	Striate cortex (17 or 18) or claustrum

Visual response of cell RPG 10C. The location of this cell's receptive field is seen in fig. 2 at the top left of the spike replicas of RPG 10C and another unit, RPG 10F. Based upon waveform and interspike interval criteria, the action potentials recorded from RPG 10C were representative of a single neuron. Maximal excitatory responses in RPG 10C were elicited with a 10 deg spot located in the left upper quadrant at an eccentricity of 40 deg from the central fixation point. Although only the neural response of RPG 10C was used to map the field, unit RPG 10F showed a good deal of receptive field overlap with RPG 10C, even though its area of maximal responsiveness was probably different. A third unit recorded during the mapping of RPG 10C is also shown in fig. 2: RPG 10H, which occasionally showed weak responses only during exploration of the upper left quadrant. The receptive fields of RPG 10F and RPG 10H were not mapped in more detail. As seen in the records to the right of the second and third visual field diagrams, the entire receptive field was considerably larger than 10 deg for RPG 10C, since weak responses were obtained from other portions of the upper left quadrant but firing was absent during testing of the upper right quadrant (bottom of fig. 2) as well as the lower hemifield. Responses remained maximal in the 10 deg area diagrammed at top left for the entire period over which the cell was tested.

The borders of the receptive field of RPG 10C were difficult to define because at a 40 deg eccentricity the area of maximal response was 5 deg to the left of the tangent screen. When the edge of the screen was extended to include the receptive field, the response of the unit decreased. Return to original conditions brought a return of the response. A decreased response was also noted after the patient was asked to shift her point of fixation 35 deg to the right along the horizontal meridian, so that retinotopically, the receptive field was located in the upper central region of the

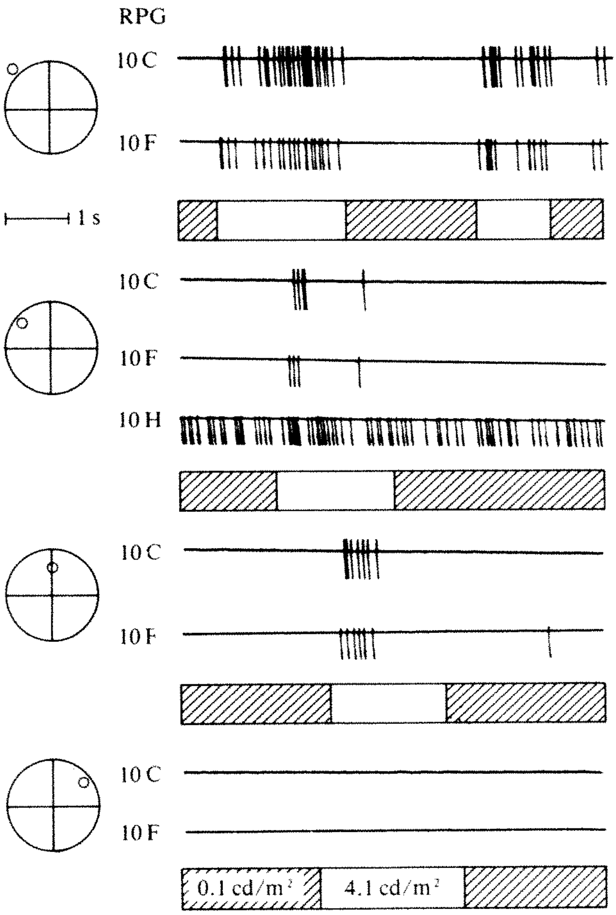

FIG. 2. Recordings from *Case 127* in the Clinical Neurophysiology Program at UCLA. *Top to bottom*: change in response with illumination of four upper hemifield areas with a 10 deg spot. Diameter of circular field is 70 deg. Periods of luminance increase are denoted by white areas in the bar below each group of unit tracings. The luminances in each case were the same as shown at the bottom. Unit discharges in this and most of the subsequent figures are the polygraph record of window discriminator output triggered by the analog unit signal, in which amplitude is not represented. Note that response could be either sustained or transient. Exact locus of upper receptive field is described in the text.

screen. That is, a 10 deg, 4.1 cd/m^2 spot projected at a 40 deg eccentricity to the *new* fixation point was now ineffective, perhaps because it now illuminated the uniform, blank area in the centre of the screen rather than some complex patterned trigger feature to the left of the tangent screen.

Further testing with fixation upon the central LED showed the receptive field had no easily detectable movement or directional sensitivity, nor orientation selectivity, and was unresponsive when ambient room lighting was increased 1.7 log units above background and a 10 × 12 deg black rectangle used to explore the upper left quadrant. Although precise definition of the receptive field borders of the unit was not possible, its activation was clearly dependent upon illumination of a restricted retinal area as demonstrated in fig. 3, where repeated tests with left upper quadrant *vs* full field illumination are illustrated.

Spontaneous activity, as shown in fig. 3A, was low; mean firing rate was 0.38 spikes/s during 225 s of spontaneous activity and appears unrelated to eye movements (m) or blinks (b). Illumination of the area plotted in the top diagram of

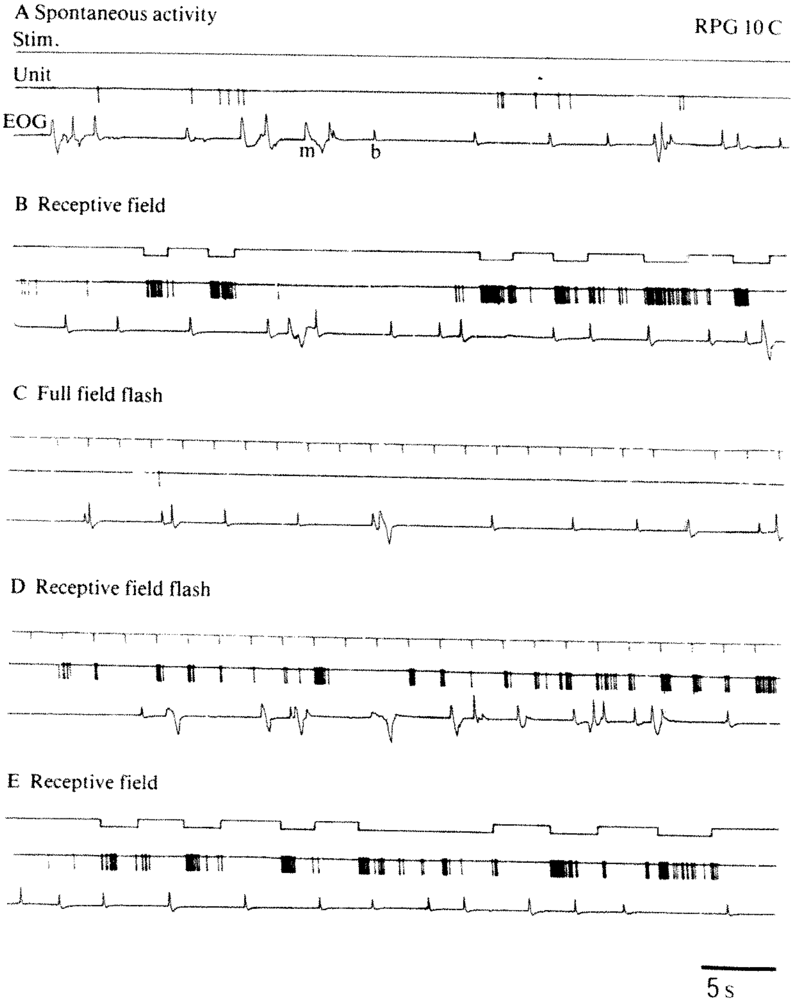

FIG. 3. Unit RPG 10C. Brief and sustained illumination of left upper quadrant receptive field *vs* full field illumination. A downward deflection in 'stim' tracings B and E denotes a 1.6 log unit luminance increment; upward deflection a return to the 0.1 cd/m² ambient level. In C and D, increase of luminance during flashes is 2.7 log units above the same ambient level. A, no luminance change; m = eye movement, b = eye blink. B, illumination of receptive field area as in A. E, repeat of B to show stability of response. EOG bandpass, 0.1 to 90 Hz. Patient fixated 1.5 log unit red point source LED in centre of field. Disc electrodes were placed above the right eye and below the left in this patient. Upward and/or right directed eye movements were recorded as an upward pen deflection, down and/or left by a downward pen deflection. The upward deflection marked by 'm' in the top trace is 100 μV.

fig. 1 with 10 deg spot 1.6 log units above background elicited the responses shown in 3B: brisk discharge for periods shorter, the same, or longer than the duration of illumination, but discharge clearly related to the stimulus, and unrelated to eye movement. This responsiveness may be contrasted with the firing rate during full field 10 ms duration flashes, 2.7 log units above background, presented at a rate of 0.5 Hz as shown in 3C. Firing was reduced during full field flashes to a rate of 0.06 spikes/s during 225 s of 0.5 Hz stimulation (less than one-sixth the spontaneous rate). A lowered firing rate was also recorded during 50 s of 2 to 5 s presentations of the 10 deg spot in the lower hemifield (not shown). When the 10 ms flash was limited to an 18 deg area centred over the receptive field, the responses seen in 3D were obtained, indicating that whatever antagonistic influence was active in 3C, it was not present when visual stimuli were limited to this area of the upper left quadrant. Some responses are distorted by blinks and eye movement, but responsiveness to the 18 deg flash during periods of steady central fixation of the LED is evident. In 3E, a return to illumination of the receptive field with the 4.1 cd/m², 10 deg spot elicited brisk responses similar to those in 3B. Note the tendency in both figs. 3B and E for responses to be sustained and in 3E, the apparent 'OFF' discharges following long duration stimuli.

The response to brief (10 ms) and sustained (1 s) periods of illumination of the receptive field is shown in fig. 4, along with 3 superimposed evoked potentials recorded during the unit discharges illustrated both in 4A and B. Responses were not

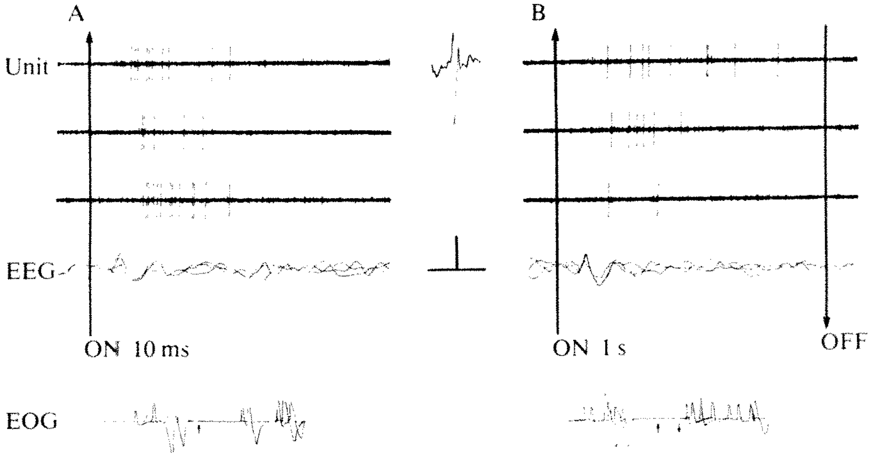

FIG. 4. Unit RPG 10C and EEG response from the same microelectrode to brief and sustained receptive field illumination. In A, oscillograph records of unit responses to flash (ON 10 ms) are not significantly different in duration to those evoked by 1 s luminance increments as shown in B (ON-OFF). Luminance increased 1.6 log unit above 1.4 cd/m² ambient level. Latency variability also occurred during sustained illumination of receptive field. EEG traces are the low pass oscillograph records from the same three responses above in A and B superimposed to show the evoked field potentials during either brief or sustained photic stimulation. EOG records are 10 s in duration showing superimposed records of peristimulus eye movements before and after the stimulus presentations which are marked by small arrows. The action potential record at centre top was recorded with a band pass of 0.3 Hz to 5 kHz, other unit records, 100 Hz to 5 kHz. Time calibrations are as shown. Amplitude calibrations: action potential, 50 μV; units, 100 μV; EEG, 200 μV; EOG, 150 μV.

always sustained, as seen in 4B. The 3 responses in 4B were chosen to show the range of variability found, and the responses in 4A show that the discharge to the 10 ms flash was sometimes of a longer duration. The mean latency of neuronal response during 11 presentations of 10 ms flash was 183 ms (SD, 19.7) while the unit response latency during 8 luminosity increases of 1.0 s duration was 197 ms (SD, 18.5, luminosity identical to flash). Superimposed EEG traces during each of the three responses in A and B illustrated reliability of the field potentials evoked by both stimuli. Latencies to the positive (upward) peak seen in both A and B were in a similar range to the 'P-100' reported from scalp electrodes in the occipital region in man during presentation of visual stimuli (*see* Jeffreys, 1977; 10 ms stimulus, $n = 9$, $\bar{x} = 106$, $SD = 4.6$; 1.0 s stimulus, $n = 12$, $\bar{x} = 102$, $SD = 3.7$). In addition, it was seen that the strength of evoked neuronal discharge was not closely related to the amplitude of evoked potentials (fig. 4, EEG), the latter occurring also in the absence of unit response (not shown). Larger amplitude flash evoked field potentials were characteristic not only of sites for which receptive fields were mapped, but also of most posterior hippocampal sites showing unit response to visual stimuli. Superimposed EOG records indicate that no eye movements or eye blinks contaminate any of the visual responses. The triphasic action potential waveform shown in fig. 3 has a duration of 0.7 ms.

Visual response of cell RPG 10E. The next cell to be described is one in which a receptive field characterization similar to the lateral geniculate nucleus was encountered. It and the cell just described (RPG 10C) were recorded from 2 separate microelectrodes in the right posterior hippocampal gyrus of the same patient at the point labelled 'RPG 10E' in the coronal section diagram at top right in fig. 5. The portion of the geniculocalcarine projection known as the external sagittal stratum (Polyak, 1957; Shoumura, 1973) is represented lateral to the hippocampal gyrus (putative connections to medial temporal regions have been added in this diagram—*see* Discussion). At top left the small area of the visual field which influenced activity of this unit is plotted in the upper left quadrant about 10 deg above the left horizontal meridian and at an eccentricity of 30 deg from the fixation point, thus showing relatively close retinotopic correspondence to the previous unit. In contrast, the firing rate of RPG 10E was much higher than that of RPG 10C at the background luminance level.

Fig. 5A illustrates the prominent sustained excitatory response obtained from this unit when a 1.0 deg spot with luminance 1.6 log units above background was projected on the receptive field for 5.0 s, during fixation of the LED at the centre of the tangent screen. In 5B, the background luminance has been increased 1.7 log units above that in 5A, resulting in a pronounced increase in baseline firing rate. When a 1 × 2 deg black rectangle 1.0 log unit below the background luminosity of 5B was placed over the receptive field, the tonic discharge of the unit is almost entirely inhibited. Notice that the firing rate is essentially zero during the placement of the black rectangle over the receptive field in 5B, whereas there is a relatively high rate of spontaneous discharge in 5A when the background luminance is 0.5 log unit less than that of the black bar. This difference could be attributed either to reduced receptor sensitivity due to light adaptation in the greater ambient luminance condition of 5B, or to a nonlinear central response. Figs. 5C and D show the onset and offset of a luminance increase similar to that illustrated in 5A, but here the oscillograph-plotted unit action potentials are displayed at a faster time base than

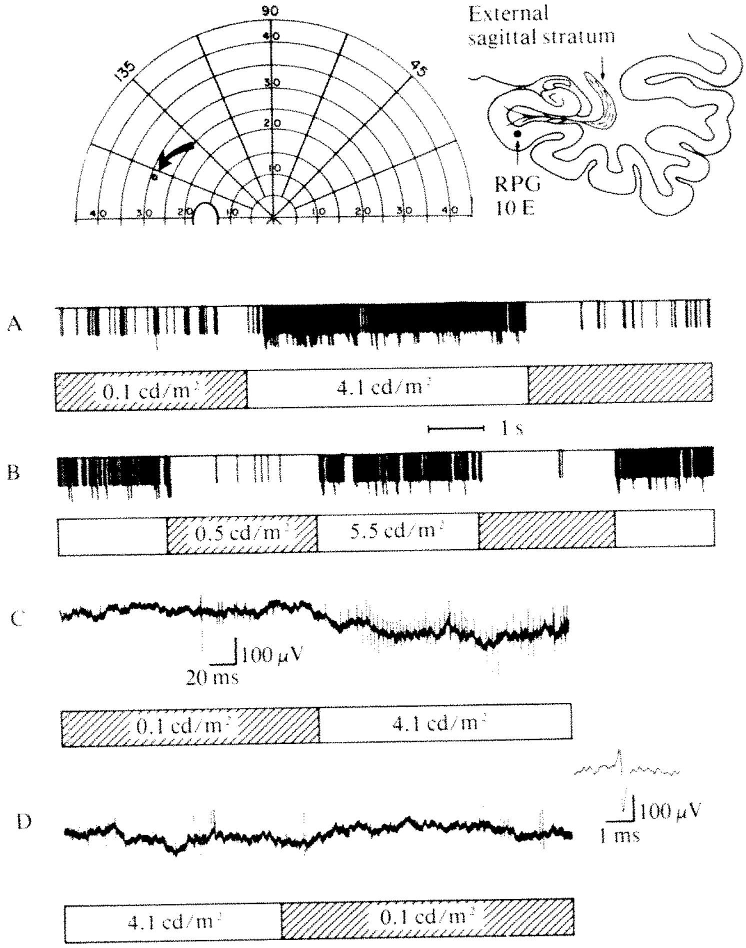

FIG. 5. *Case 127.* Receptive field location and response pattern of unit RPG 10E. Arrow in visual field at top left indicates 1 deg receptive field in left upper quadrant. At top right the location of the electrode from which RPG 10E was recorded is plotted on a diagram of a coronal section of the temporal lobe at the level of the posterior hippocampal formation. In A and B, changes in unit discharge rate (as represented by the output of a window discriminator) during increases and decreases in luminosity are marked by the bars below the unit records. Visual stimuli were, in A, a 1 deg spot projected on the tangent screen and in B a 1 × 2 deg black bar placed over the receptive field. Note that the ambient luminance level in A was low and in B was high. In C and D the onset and offset of a stimulus identical to that shown in A is shown along with an oscillograph recording of the unit which is represented by window discriminator output in A. RPG 10E had a positive-negative biphasic waveform as indicated by the action potential insert at the bottom right. A second, monophasic, positive unit is seen on the traces of C and D but is easily discriminated from RPG 10E.

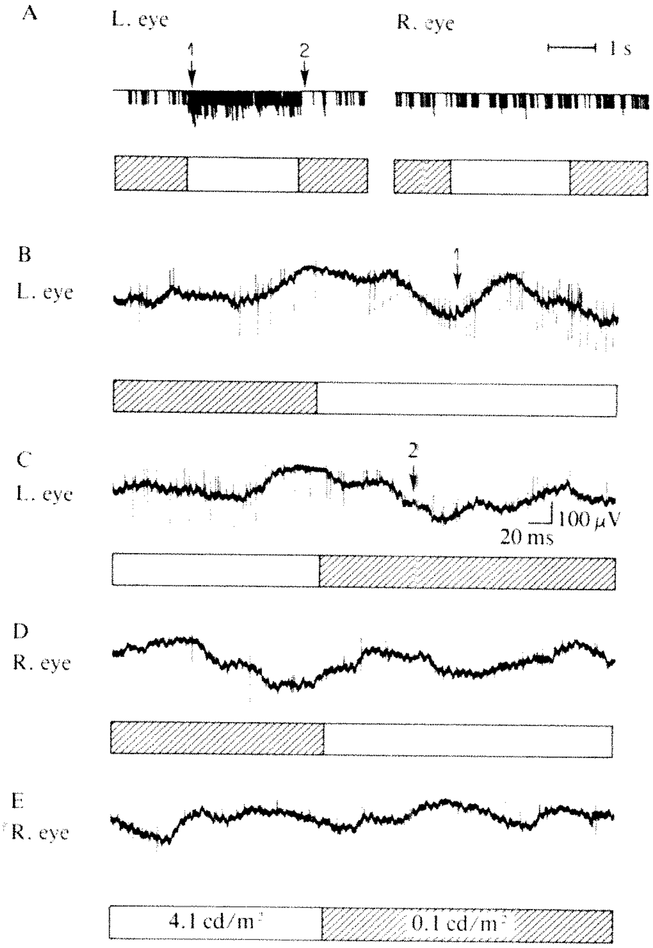

FIG. 6. *Case 127.* Monocular responsiveness of unit RPG 10E. In A, discriminated output record of unit activity shows a response when left eye is open and right eye occluded but no response when right eye is open and left is occluded. In B to E are oscillograph records of onset and offset of luminance changes from the same stimuli plotted in A. Arrows at 1 and 2 in A indicate burst of activity at onset and absence of activity at offset in record A, and at the same points in B and C.

the polygraph records in 5A, in order to show the discharge rate more precisely, as well as the adaptation of the response after its onset. The 0.7 ms duration of the positive-negative biphasic action potential wave form is illustrated at bottom right of fig. 5.

Unit RPG 10E responsivity appeared to be monocular. When the right eye was occluded and the left fixated the LED at the centre of the tangent screen, a brisk neural discharge accompanied illumination of the receptive field (fig. 6A, *left*). When the left eye was occluded and the right viewed the LED, no change in unit activity accompanied luminance changes in the receptive field (fig. 6A, *right*). However, a binocular contribution cannot be ruled out because no quantitative comparison between left monocular and binocular visual stimulation was made. The onset of receptive field illumination with the left eye open was followed by a burst of firing, and then rapid adaptation, as marked by the arrows labelled 1 (figs. 6A and B), while the offset of illumination was followed by a brief absence of firing, as marked by the

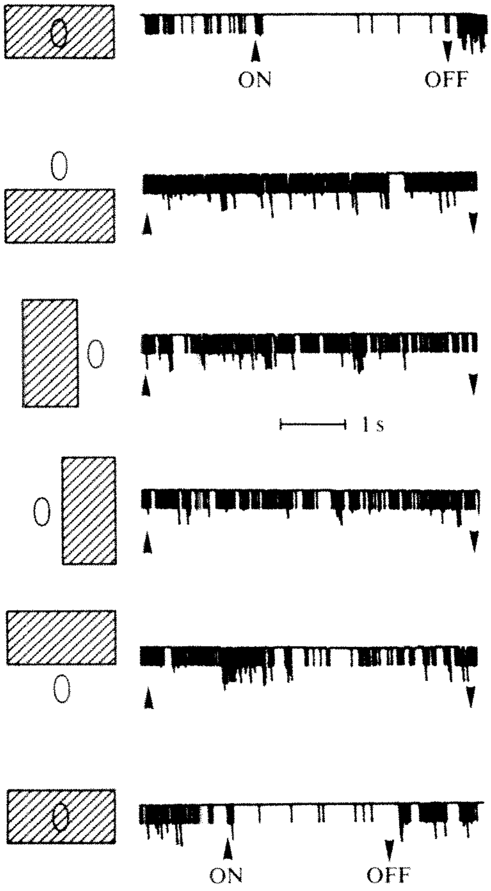

FIG. 7. *Case 127*, unit RPG 10E. Absence of change in unit activity during black bar stimulus presentation in region surrounding receptive field. Bar size: 1 × 2 deg receptive field 0.25 × 0.50 deg with ambient luminance of 5.5 cd/m^2, and bar luminance of 0.5 cd/m^2. Arrows up and down mark placement of the bar either on or off the receptive field in the top and bottom records. Arrows mark the point of shift in position of bar from bottom to left to right to top in middle four records. Discriminator output only is shown in this and subsequent records.

arrows labelled 2 (figs. 6A and C). This acceleration and offset inhibition occurred often during stepwise luminance increase or decrease. No change in unit discharge occurred during receptive field illumination with the right eye open (figs. 6D and E), although the patient reported that she could detect the small spot of light in her left visual field while fixating the central LED with either the right or the left eye, consistent with the fact that the monocular temporal crescent is seldom reached before an eccentricity of 50 deg or more.

Receptive field organization of RPG 10E. The limited area of this receptive field is schematically illustrated in fig. 7, where the small ellipse represents the receptive field and the cross-hatched rectangle, a black rectangle held either directly over or else adjacent to the receptive field when background luminance was high. The prominent decreases in firing at the top and bottom of the figure when the black rectangle covers the receptive field, contrasts with the absence of an effect when the bar is adjacent to the receptive field.

No evidence for an antagonistic centre surround receptive field organization was obtained in the low ambient illumination condition. When a 4 deg spot was projected on the centre of the receptive field, the response strength was the same as to the 1 deg spot, not weaker. Under a high ambient illumination condition, only one test sensitive to surround antagonism was performed. That test was positive, as shown in fig. 8, but the reliability of the response was not established. In the top record of fig. 8 a 1 × 2 deg black bar completely inhibited unit firing whereas in the bottom record, a 9 × 11 deg black surface produced a comparatively weak (but significant) reduction in firing rate. The actual dimensions of the antagonistic surround (dotted line) as illustrated diagrammatically to the left of the unit records in fig. 8 are unknown since time constraints did not allow more precise mapping of its borders. However, the extent of the surround was probably less than the 9 × 11 deg black surface as indicated by the relative lack of change in response in the middle four records of fig. 7, where a black bar was placed within 1 to 2 deg adjacent to the receptive field. The size of the receptive field centre also varied with background luminance levels. With the 0.1 cd/m^2 background, the excitatory region was 1.0 deg in diameter, with no easily discernible deviation from a circular shape. During 5.5 cd/m^2 background illumination, the central region was smaller, with a vertical dimension of 1.0 deg and a horizontal dimension of 0.5 deg. When a light or dark edge was swept manually across the receptive field, response strength was the same regardless of orientation, direction or velocity of movement.

Fig. 9 allows comparison of unit RPG 10E with unit RPG 10C, described earlier (fig. 3). The raster (fig. 9A) and PSTH (fig. 9B) records indicate a latency of 37 ms for RPG 10E to brief, full field photic stimulation 1.3 log units greater than used in fig. 3. This latency is substantially shorter than the nearly 200 ms latency of RPG 10C in

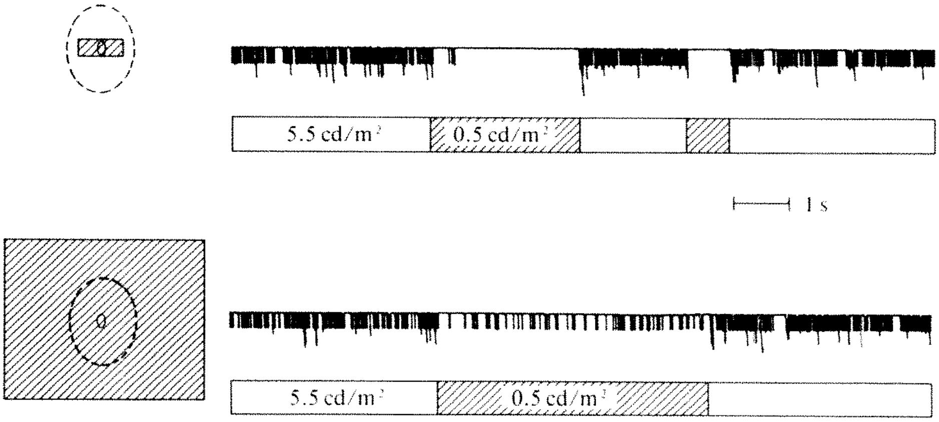

FIG. 8. *Case 127.* Antagonistic surround of unit RPG 10E. In *top* record, unit activity is completely suppressed when a 1 × 2.5 deg black bar was centred on the receptive field. Relative contrasts are indicated in bar below unit record. Unit activity is only partially suppressed when a 9 × 11 deg black field is centred over the receptive field. True size of the antagonistic surround was not determined and is only estimated in the diagram.

response to brief receptive field stimulation, but the responses of the two units cannot be directly compared since a decrease in latency would be expected because the luminosity of the flash used to evoke the response from RPG 10E was greater. Note, also, that the vigorous response of the unit to increase in full field luminosity indicates the weakness of any inhibitory surround mechanism under conditions of low ambient illumination in contrast to the high background illumination conditions of fig. 8. In fig. 9C, the background luminance was increased 1.0 log unit above that in 9A and B, resulting in a great decrease in responsiveness, when stimulus and background contrast were reduced. The inhibition response could also be due to surround antagonism effects present only during higher ambient illumination.

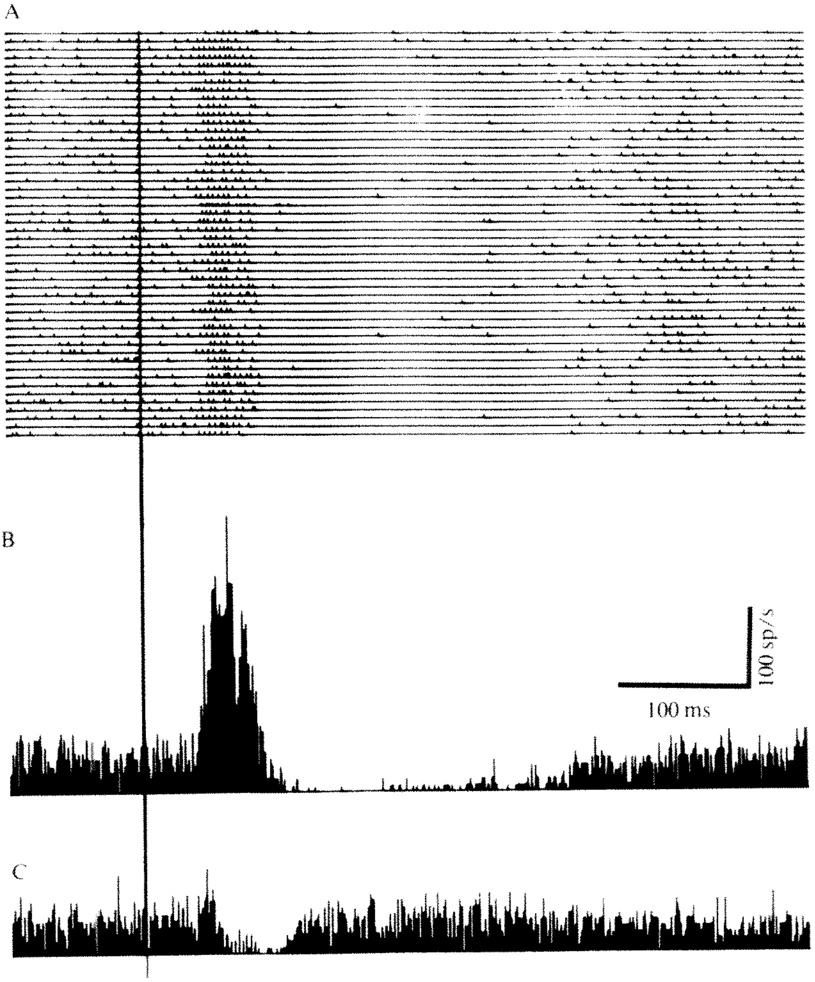

FIG. 9. Latency of response of unit RPG 10E to brief full field photic stimulation. A, raster display of 50 responses to flash which occurs at black vertical line. B, peristimulus response histogram to 136 iterations of the same stimulus. C, response to 127 presentations of the same stimulus flash after background illumination level has been increased 1.0 log unit.

Although not apparent here, during nonstimulated periods in the low background illumination condition used in A and B, the firing rate of the unit was 23.3 spikes/s while during high level background illumination (C), the firing rate increased to 42.3 spikes/s (10 s sample for each).

In summary, unit RPG 10E recorded in the parahippocampal gyrus, appeared monocular, showed initially adapting but sustained excitatory responses in the low mesopic to low photopic range during illumination of its roughly circular, relatively small and peripheral receptive field, and it appeared to have an antagonistic surround. Further, the unit showed no evidence of habituation to repeated visual stimuli, had a short latency, and in spite of prolonged testing with slits, bars and edges, revealed no orientation or directional selectivity. All of these response characteristics are typical of receptive fields recorded from the lateral geniculate nucleus in animal studies.

A fifth unit, RPG 10EP was recorded on the same electrode, as can be seen in figs. 5 and 6. This unit also showed visual responsiveness, but the boundaries of its receptive field were not mapped. The receptive field of a sixth unit, RPG 10J, was mapped in the upper left quadrant. The centre of its receptive field was 5 deg above the horizontal meridian and 10 deg to the left of the vertical meridian. It subtended approximately 10 deg horizontally, and 1 deg vertically. In background light conditions, a light slit orientated horizontally and moved up or down across the field elicited a brisk phasic response, while back and forth movement of the same bar orientated vertically was ineffective. Response was binocular with indeterminate dominance. With a 1.0 log unit increase in background luminance, a large black bar moved up or down through the field with the edge orientated horizontally was quite effective in evoking brief, transient responses. The unit was lost before its receptive field could be studied further.

Occipital Lobe Units

Using diffuse flash stimuli, 11 of 12 units recorded from the occipital lobe of Case 122 were found to be visually responsive. The electrodes were implanted in these sites because the patient experienced partial complex seizures preceded by auras of unformed visual sensations such as flashing coloured lights (Babb *et al.*, 1981). During testing, several of these units were found to be responsive to patterned stimuli of several spatial frequencies (checkerboard reversals), but only the response to diffuse photic stimuli will be described here as a comparison with medial temporal lobe units. Fig. 10 shows that the latency of response in the top and bottom PSTHs recorded from the right circumstriate cortex is similar to that recorded from the posterior hippocampal gyrus (RPG 58HH, middle PSTH) in the same subject. The onset latencies in the occipital lobe units are 42 and 45 ms while that in temporal lobe was 47 ms. PSTH response morphology of the posterior hippocampal gyrus cell is generally comparable to the responses of the occipital lobe cells. The shortest latency of the 11 responsive occipital cortex cells was 31 ms; the mean latency was 63.6 ms (range, 31 to 110 ms, SD, 25.1).

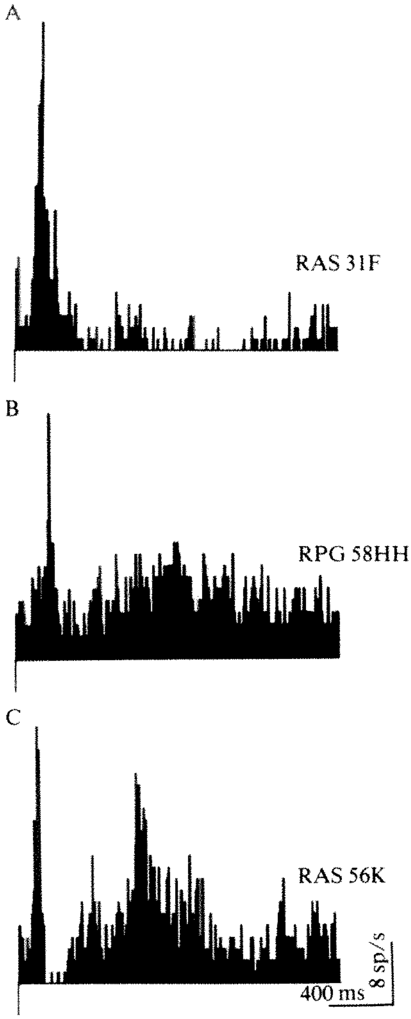

FIG. 10. *Case 122.* Comparison of occipital cortex and hippocampal gyrus responses to 256 full field 10 ms flashes, 2.7 log units above 0.1 cd/m² ambient luminance. A and C, right anterior striate cortex unit poststimulus histograms. B, right posterior hippocampal gyrus unit response recorded simultaneously from same patient.

Visually Responsive Thalamic Units

Responses to brief, diffuse photic stimulation from one of the 2 cells localized in the lateral geniculate nucleus and from 2 of the 3 in pulvinar nucleus are shown in fig. 11. In 11A the response latency of a lateral geniculate unit is 27 ms, as was the latency of a second unit not shown. In 11B, the response latency of a pulvinar cell is 30 ms and the latency of a second cell from another patient shown in 11C is 27 ms. Two other pulvinar cells were not responsive. These latencies are comparable to the 30 to 40 ms latencies commonly recorded in the hippocampal gyrus, although much shorter than gyrus unit RPG 10C, which had a latency of 200 ms. These comparisons of latencies of hippocampal gyrus unit response with visual cortical

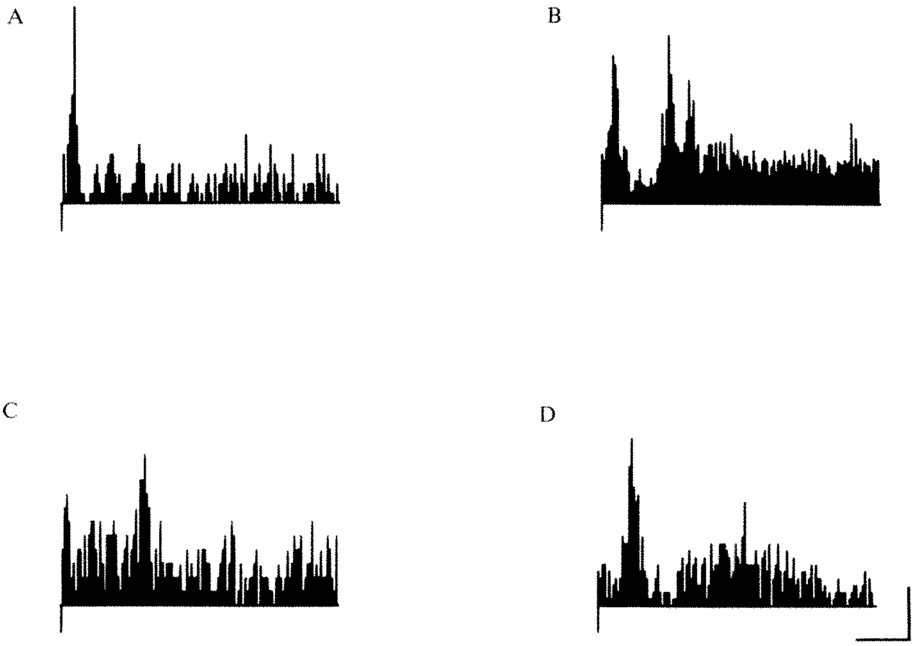

FIG. 11. Examples of visually responsive thalamic units. All PSTHs are summations of responses to brief flashes of a Grass PS-2 photostimulator at ×4 intensity. A, *Case 72*. Left lateral geniculate nucleus unit response, 150 stimuli. B, *Case 63*. Right pulvinar unit response, 150 stimuli. C, *Case 65*. Left pulvinar unit response, 200 stimuli. D, *Case 65*. Right posterior hippocampal gyrus response, 200 stimuli. Note longer latency (88 ms) characteristic of hippocampal gyrus response. Calibrations: amplitude in A = 2.5 spikes/s, B = 25.0 spikes/s, C, = 2.5 spikes/s, D = 5.0 spikes/s; time = 200 ms.

and subcortical neurons indicate the heterogeneity of sensory input to the posterior limbic cortex, and suggest that neurons in the hippocampal gyrus may be activated either by short latency subcortical visual afferents, or may receive longer latency inputs *via* corticocortical connections.

DISCUSSION

The results of the present study establish, at a neuronal level, the availability of visual information to structures within the human medial temporal lobe, with the majority of visually responsive neurons being located in the posterior parahippocampal gyrus. Like the visual neurons of the inferior temporal lobe, some of the cells in this region respond strongly enough to allow receptive field mapping. However, the two regions differ in that the hippocampal gyrus receptive fields appear visuotopically organized whereas inferior temporal neurons are not (Gross *et al.*, 1979). Despite this visuotopic relationship, the heterogeneity of receptive field characteristics of the units sampled in this study suggests the influence of more than one source of visual afferents. The receptive field of one cell, RPG 10E, exhibited many characteristics of cells of the lateral geniculate nucleus (Kuffler, 1953), cell RPG 10J was similar to cells of striate cortex (Hubel and Wiesel, 1977), while the response pattern of RPG 10C demonstrated more complex trigger features. The significance of the heterogeneity of receptive field types at a single site in the medial temporal lobe will be considered in the light of: (1) previous studies of hippocampal formation visual response; (2) possible anatomical sources of visual input to this brain region; and (3) the functional significance of visually responsive temporal lobe neurons.

Previous Studies of Visual Response in Medial Temporal Lobe

Investigations of single unit visual response have been carried out in monkey, rabbit and rat. The results most comparable to the present study came from the work of MacLean *et al.* (1968) with squirrel monkeys. Using photic stimuli similar to those in our screening study, that is, diffuse, full field flashes of 2 to 5 s luminance changes, they recorded responses from 6.5 per cent of 279 cells located in the posterior hippocampal gyrus. One-half of the responsive cells showed sustained responses. The mean latency for all responses was 58.7 ms. In the present study, 20 per cent of 96 posterior hippocampal gyrus cells were responsive, one-third showed sustained responses, and the mean latency was 71.8 ms. The categorization of unit responses in sustained *vs* transient classes has been found to be useful in studies of the mammalian visual system in both cat (Enroth-Cugell and Robson, 1966; Cleland *et al.*, 1971; Ikeda and Wright, 1975*a*, *b*) and monkey (Gouras, 1968; de Monasterio, 1978). How this response differentiation relates to the X *vs* Y or linear *vs* nonlinear spatial summation distinctions in animals (reviewed by Lennie, 1980) was not determined here but should receive further study since the distinction appears to be useful in human visual processing as well (Legge, 1978).

In another study of visual responsiveness in this region, Desimone and Gross (1979) recorded from 56 multiunits in parahippocampal gyrus of paralysed macaques. They found about half the units were exclusively responsive to visual stimuli and one-third were responsive to both visual and somaesthetic stimuli. In one figure, they showed an example of a sustained visual response recorded from a single cell which appears similar to the response of unit RPG 10C (fig. 2). They reported that units in this region are much more difficult to drive than those of the inferior temporal cortex, because they have large diffuse receptive fields and habituate very rapidly. The receptive fields of these cells usually cross the vertical meridian and include the fovea. Recording in the inferior temporal cortex, they found the cells more responsive to three-dimensional objects than to single visual stimuli. In the present study, no response bias toward three-dimensional objects as compared with simple visual stimuli was detected. Gross *et al.* (1979) used visual display of objects (for example, brushes, springs, etc.) in testing responses of inferior temporal cortex cells in awake, behaving macaques. They found 67 per cent of the cells were responsive; 52 per cent responded only when the object was actively fixated. The receptive fields of the present study did not include the fovea, and tests of object fixation and (in RPG 10C) of receptive field fixation were negative. In sum, the data from the parahippocampal gyrus of both squirrel monkey and macaque are consistent with the presence and type of visual responsiveness in the human parahippocampal gyrus. Our results are also consistent with Desimone and Gross (1979) showing that parahippocampal visual responses are unlike those in the inferior temporal cortex.

In the hippocampus proper (not hippocampal gyrus), MacLean *et al.* (1968) found no visually responsive cells in the squirrel monkey, in spite of extensive testing, whereas 17 per cent of the 99 hippocampal and subicular units tested in the present study were visually responsive. In studies of nonprimate hippocampus, visually responsive units were prominent in both rat (Segal, 1974; Miller and Groves, 1977) and rabbit (Lidsky *et al.*, 1974). It is of interest that in the study of Lidsky *et al.* (1974), the mean latency of flash evoked unit responses in hippocampus was 22.5 ms, and the shortest latency was 16 ms, reducing the likelihood that the source of the response was *via* a multisynaptic cortical relay. A second example of a short latency visual input to hippocampus has been provided in rat by Vastola (1982). These studies support the existence of a subcortical or fast oligosynaptic cortical relay to medial temporal lobe and hippocampal formation.

Possible Sources of Visual Input to Medial Temporal Lobe and the Hippocampal Formation

The human optic radiations. Several hypotheses can be entertained as to the sources of visual input for the various types of visual unit responses recorded in the medial temporal lobe. The first is that they may represent recordings from optic radiation fibres which project from the lateral geniculate nucleus to striate cortex *via* the detour through temporal lobe white matter known as Meyer's loop. This portion of the optic radiation is made up of retinotopically organized fibres representing the superior hemifield, which initially sweep approximately 2.0 cm rostrally and then bend laterally back and ventrally beneath the inferior horn of the lateral ventricle. After circumventing the ventricle, the fibres project caudally to the calcarine fissure through the white matter of the temporal lobe in a wide band known as the external sagittal stratum. Probst (1906, p. 140) provided early experimental Marchi data in a patient with central lateral geniculate and pulvinar degeneration. It showed that a horizontal limb of the sagittal stratum extended medially from the lateral temporal lobe and deeply into the white matter of the hippocampal gyrus. The greatest excursion into the temporal lobe appears to be made by fibres from the lower peripheral regions of the retina since visual field defects which often accompany anterior temporal lobectomy usually occur in the upper contralateral quadrants, and seldom extend to central visual areas (Cushing, 1922; Van Buren and Baldwin, 1958; Babb *et al.*, 1982).

Several authors have come to the same conclusion using normal human material (Pfeifer, 1925; Polyak, 1957; Putnam, 1926; and Redlich, 1905) but none has found evidence of fibres terminating in the cortex of the hippocampal gyrus. Shoumura (1973) examined the trajectory of the optic radiation with Nauta degeneration in the cat, and found fibres representing Meyer's loop, but none terminating in the hippocampal gyrus. The presence of optic radiation fibres in the medullary core of the hippocampal gyrus provides a ready explanation for the origin of unit RPG 10E since its receptive field is very similar to that of lateral geniculate neurons studied in monkey and cat (Kuffler, 1953; Wiesel and Hubel, 1966). The most parsimonious interpretation of the RPG 10E receptive field is that the recording was from an optic radiation fibre, since there are many studies describing fibres passing through this region but it is generally accepted that the geniculocalcarine pathway has no temporal lobe terminations or extrastriate collaterals (*see* Wilson and Cragg, 1967). If this unit was the axon of a lateral geniculate neuron, it indicates that most of the basic features of the lateral geniculate reported in animals are shared by humans. However, there is one contradictory study which carefully examined the trajectory of the optic radiation in the squirrel monkey (MacLean and Creswell, 1970). Using the Nauta method, they reported degeneration leading into the white matter of the posterior hippocampal gyrus after lesions of the lateral geniculate nucleus, where 'A number of fine fragmented fibres could be followed further into the cortex, running among and in some instances seeming to make contact with nerve cells.' (MacLean and Creswell, 1970, p. 269). It is this study which provided us with the basis for portraying the fibres from the sagittal stratum in fig. 5 as projecting into the posterior hippocampal cortex.

Lateral geniculate collerals or projection. If MacLean and Creswell are correct it is possible that the short-latency responses recorded are not optic fibres, but that the responsive hippocampal gyrus units reported in the present study may represent cells that receive collateral axons branching medially from the horizontal limb of this portion of the optic radiation. Perhaps because the MacLean and Creswell study is counter to the generally accepted concept of the geniculocalcarine projections, it is seldom cited, and no replication has been reported by another laboratory using contemporary anatomical methods rather than degeneration after lesions of the lateral geniculate. Nevertheless, several factors from the present study suggest RPG 10E may have been a hippocampal gyrus projection neuron rather than a fibre of passage.

Since the units in the present study were recorded using platinum microwires 40 μm in diameter it might be assumed that the population of units recorded would be biased toward large somata rather than axons. The units for which receptive fields were mapped also showed waveform characteristics of a somal or dendritic nature not axonal (Bishop *et al.*, 1962). Their duration was 0.7 ms or greater, RPG 10E showed a notch on the initial wave of the majority of action potentials which may have represented an A/B break, a second visually responsive unit on the same electrode showed a notched triphasic waveform, and RPG 10C was triphasic. The long duration over which these units were held (several hours) also suggests a somatic origin. Although none of these waveform characteristics allows positive identification of a unit as somatic, they are consistent with that conclusion.

The monocular, circular, centre surround organization of the receptive field of unit RPG 10E, plus its relatively short response latency all suggest a thalamic source. The only deviation from classic lateral geniculate response properties is the apparent direct relation between full field luminosity and firing rate. Hubel and Wiesel (1977) have emphasized that background increases in luminosity produce only a weak response from lateral geniculate cells because of the antagonistic action of the inhibitory surround (but *see* the 'ambient cells' described by Spear *et al.*, 1977). If the unit was an axon of a lateral geniculate neuron, it may represent a different class of geniculate neurons found in humans but poorly represented or not found in lower primates. Alternatively, if the unit is a hippocampal gyrus neuron activated by lateral geniculate collaterals, the apparent direct relation between luminance and firing rate may be a function of integrating or convergence properties of hippocampal formation neurons.

In addition to the classical Meyer's loop trajectory, there is a recent report of an alternative dorsal lateral geniculate projection to a cortical region adjacent to the posterior hippocampal gyrus in the macaque by Yoshida and Benevento (1981). Injections of labelled methionine completely confined to the lateral portion of the dorsal lateral geniculate nucleus resulted in transport within and anteroventral to the inferior occipital sulcus extending to the occipital temporal sulcus. This finding is in opposition to the general assumption that the geniculate projects solely to area 17 in primates (Garey and Powell, 1971; Hendrickson *et al.*, 1978; Polyak, 1957; Wilson and Cragg, 1967).

All the above data support the notion that in primates there may exist collaterals from the geniculostriate pathway that terminate on neurons in the parahippocampal gyrus. Perhaps the most compelling observation in favour of this hypothesis, however, is the fact that operative radiographs showed that the tips of the microelectrodes from which these receptive field units were recorded were within 1.0 mm of one another. If it is assumed that the 'geniculate-like' unit (RPG 10E) was recorded from one of a bundle of optic radiation fibres, then the other receptive fields from units recorded on adjacent microelectrodes should also represent fibres from that bundle. The receptive fields of the other two units strongly suggest origins other than lateral geniculate nucleus. The variability in receptive field characteristics observed is more likely to occur in a cortical site receiving convergent inputs than in a fibre tract. What then is the source of visual input to these other posterior hippocampal gyrus units?

Pulvinar nucleus projections. The third pathway, which assumes direct pulvinar innervation of the hippocampal gyrus, is not a likely candidate. The pulvinar, along with the lateral geniculate, receives direct retinal afferents as reported by Berman and Jones (1977) and as reflected by the 27 ms latencies recorded in both these nuclei in the present study. Benevento and Rezak (1976) and Trojanowski and Jacobson (1976) have described projections from medial pulvinar to the medial temporal lobe. However, they found that afferents to medial pulvinar are from multimodal areas of the deep layers of the colliculi, while areas of the pulvinar receiving visual afferents project to occipital, not temporal cortex.

Corticocortical afferents. A fourth anatomical source of visual input to the hippocampal formation has been described by Jones and Powell (1970), Seltzer and Pandya (1976) and Van Hoesen and Pandya (1975). It consists of a multisynaptic trajectory from striate cortex through prestriate cortex to area TF and finally entorhinal cortex in the macaque. The origin of input to RPG 10C may be the corticocortical pathway described by Seltzer and Pandya (1976). The complex response characteristics plus the long 200 ms latency is consistent with an input which has received a high degree of preprocessing in primary and circumstriate visual cortices. This cell also differed from the others in that its complete receptive field extended outside of the upper left quadrant, to the extent that spontaneous firing rate was decreased by illumination of the lower left quadrant. Thus, it showed a retinotopic relationship to the other cells on the basis of excitatory response but not of inhibitory response.

In addition to this multisynaptic cortical pathway, a striate cortex projection which returns to the lateral geniculate from layer VI has been demonstrated (Gilbert and Kelly, 1975; Kawamura *et al.*, 1974; Updyke, 1975). Stimulation of specific layers of lateral geniculate can activate these neurons antidromically. RPG 10J was binocular, showed a linear, horizontally orientated receptive field, and was movement sensitive. In the macaque this would represent activity of cortical origin, perhaps the descending axons of a lamina VI striate cortex neuron projecting back to the lateral geniculate nucleus. In order for the latter to be a viable choice, the return projection to lateral geniculate must follow the optic radiation very closely, maintaining a retinotopic relationship to geniculocalcarine fibres. Although the return trajectory of this pathway is unknown, the receptive field of the unit would appear appropriate since long narrow receptive fields like that of RPG 10J are found in lamina VI (Gilbert, 1977; Gilbert and Wiesel, 1979).

A third telencephalic but nonneocortical source of visual input to hippocampal gyrus is the claustrum. Amaral and Cowan (1980) found ventral cells of this structure filled after HRP injections in the subiculum and hippocampal gyrus but not hippocampus. They also described the projection as being topographical. Olson and Graybiel (1980) and Sherk and LeVay (1981) have described retinotopic visual receptive fields in dorsal claustrum which in the latter study, respond maximally to long stimuli of specific orientation. Both studies report that lamina VI of the striate cortex provides input to the claustrum. Together these studies suggest a source of visual input to the hippocampal gyrus that is known to exist in lower animals, and which would predict the receptive field properties of one of the neurons recorded in the present study (RPG 10J).

Finally, it is important to remember that these proposed sources of visual input to the responsive units described here are not mutually exclusive, and it is likely that several are represented.

Functional Significance of Visually Responsive Temporal Lobe Neurons

On the basis of the anatomical analysis above, it is likely that the receptive fields mapped in the hippocampal gyrus receive inputs from both subcortical and cortical portions of the central visual system, given their receptive field characteristics and latency data. If a subcortical projection to the hippocampal gyrus is present, it offers a means for limbic areas to sample visual information at *two* levels of processing: at an early stage from thalamus and a later more fully analysed stage from cortex.

In connection with the longer latency inputs, several hypotheses concerning the importance of the medial temporal lobe and hippocampal formation in relation to memory and in the generation of endogenous potentials have been presented by Halgren *et al.* (1980, 1982). Based upon neural correlates of cognitive behaviour relevant to memory processes, they emphasize the significance of sensory information to the functional role of the hippocampal formation in memory formation and retrieval. This could involve comparisons of ongoing sensory events with past events stored in association cortex that are assessed by hippocampal formation. This area of the temporal lobe is the same which has long been identified as crucial to the establishment of new memories (Scoville and Milner, 1957). In order to determine if a functional correlate of memory processing could be found by recording unit activity from the medial temporal lobe, Halgren *et al.* (1978*a*) presented patients in the Clinical Neurophysiology Program at UCLA a visual Delayed Match to Sample task, presented as slides from a projector. Out of the 256 cells recorded, 15 per cent responded with changes in firing to every slide presented, regardless of whether they were new or old, remembered or forgotten. The majority of these visually responsive units were located in the posterior hippocampal formation and are probably from the same population as the visually responsive cells described in the present study. The rest of the units responding during behaviours were all located in the parahippocampal gyrus. Most of them fired during slides requiring choice behaviour by a patient, but had no relation to the memory aspect of the task. Five hippocampal gyrus cells did fire strongly during recall of recent events, but not necessarily to the visual memory task being employed. The most striking example was one unit which fired only when the patient was asked to remember the spatial aspects of his hospital room and ward. This cell may have been related to a class of hippocampal cells studied by O'Keefe (1976) in rats. These cells only fire when an animal is at a certain 'place' in its environment. It is assumed that the entire sensory aspect of the environment viewed from that point is the 'trigger feature' for that cell.

Unlike a traditional receptive field, the excitatory area does not move with the eye of the animal, it remains fixed in the environment, much as the receptive field of unit RPF 10C did not move to the centre of the tangent screen in the present study, when the patient moved her fixation point 35 deg to the right. In this particular case, the lack of response during fixation of a different point may have been due to something as simple as reduced pattern input on that area of the retina, or alternatively, it may have been the lack of viewing a fixed spatial array which was required to coincide with the receptive field in order for a response to occur. In either case, the *position* of the stimulus was crucial since full-field stimuli were ineffective in eliciting any response.

In conclusion, these studies of visually responsive neurons in the human hippocampal formation provide evidence of diverse visual information being projected to a structure which is known to be important for visually determined memory tasks. This convergent visual information would have obvious utility for the complex memory functions performed by the human hippocampal formation.

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BLOOD PRESSURE AND VASOPRESSIN IN PROGRESSIVE AUTONOMIC FAILURE

RESPONSE TO POSTURAL STIMULATION, L-DOPA AND NALOXONE

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SUMMARY

We showed previously that patients with progressive autonomic failure with multiple system atrophy (MSA) failed to excrete a water load while they were standing, suggesting abnormal postural regulation of vasopressin release The rise of plasma arginine vasopressin (AVP) with upright posture is modulated by central dopamine and opioid receptors. Patients with MSA may have depletion of brain dopamine and opioid peptides. We measured the plasma levels of AVP in patients with MSA and control subjects during postural stimulation by head-up tilt and the inhibition of this rise in AVP by L-DOPA (dopamine precursor) and naloxone (opiate antagonist). Since L-DOPA and naxolone can alleviate hypotension, we also studied the effects of these agents on orthostatic hypotension. Plasma AVP concentration of normal subjects rose progressively over 90 min of head-up tilt and this postural rise in AVP was abolished by L-DOPA and naloxone. Patients with MSA had similar levels of AVP while horizontal. However, they showed a severely blunted postural AVP response since their levels rose to only 10 per cent of the rise in the normal subjects despite the additional stimulus to AVP secretion of considerable postural hypotension. They also showed no inhibition of AVP secretion by L-DOPA or naloxone. Naloxone did not alter the blood pressure of either group. Although L-DOPA did not change the blood pressure of normal subjects, it lowered it in patients with MSA both while they were horizontal and tilted. In conclusion: (1) the postural stimulation of AVP release is blunted in MSA; (2) this postural rise in AVP is not inhibited by a dopamine agonist or opioid antagonist in MSA suggesting loss of dopaminergic and opioid pathways involved in AVP release; (3) endogenous opioids do not contribute to orthostatic hypotension in MSA; (4) patients with MSA are supersensitive to the hypotensive effects of an acute L-DOPA infusion.

INTRODUCTION

Patients with progressive autonomic failure with multiple system atrophy (MSA) suffer from severe and often incapacitating postural hypotension (Shy and Drager,

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1960). We showed previously that they have profound abnormalities in body fluid homeostasis (Wilcox *et al.*, 1977; Wilcox, 1982). One of the abnormalities identified in patients with MSA is an inability to excrete a water load normally while they are standing (Wilcox, Aminoff and Penn, 1974). Moreover, standing causes the release into the urine of a substance which has biological antidiuretic activity. This suggests abnormal postural regulation of vasopressin release in MSA, but there are no previous studies of plasma arginine vasopressin (AVP) levels in patients with this condition. These findings may be therapeutically important because the blood pressure of patients with MSA is abnormally sensitive to changes in body fluids (Wilcox *et al.*, 1977; Wilcox, 1982).

Plasma AVP levels normally rise in response to an increase in the tonicity of blood perfusing the hypothalamus or to a reduction in stretch in the 'low pressure' cardiovascular system within the thorax. The intrathoracic stretch receptors are believed to mediate the rise in plasma AVP that occurs on standing or head-up tilt. These receptors are connected by the vagus nerve to the vagal nucleus and thence to the nucleus of the tractus solitarius which projects directly to the paraventricular nucleus (Ricardo and Koh, 1978) and receives both oxytocin- and vasopressin-containing projections from this nucleus (Swanson and Sawchenko, 1980). The nucleus of the tractus solitarius is richly innervated by catecholamine-containing neurons (Dahlström and Fuxe, 1964; Palkovits and Jacobowitz, 1974) and contains abundant opiate receptors (Atweh and Kuhar, 1977). We have found that the rise in plasma AVP that occurs when normal subjects are tilted head upwards is inhibited by infusion of the dopamine percursor L-DOPA or the opiate antagonist naloxone. This indicates that the postural regulation of AVP release in man depends upon activity in both dopamine and opiate-regulated pathways. Patients with MSA have extensive structural lesions within their brainstem and hypothalamus; neurochemical techniques show depletion of dopamine from these regions (Spokes *et al.*, 1979). Although opioid peptide levels have not been studied in patients with MSA, a preliminary report of marked decreases in metenkephalin in the ventral tegmental areas of brains from patients dying from Parkinson's disease has been published (Taquet *et al.*, 1981). Thus, the postural regulation of AVP release may be impaired in patients with MSA because of loss of central dopamine and opioid pathways.

In the present study, we have tested this hypothesis by comparing the AVP response to head-up tilt in normal subjects and patients with MSA, both under control conditions and during infusion of either L-DOPA or naloxone. Since chronic L-DOPA treatment can alleviate hypotension in MSA (Aminoff *et al.*, 1973) and naloxone can alleviate hypotension in shock (Faden and Holaday, 1979; Holaday and Faden, 1980; Peters *et al.*, 1981), we also studied the acute effects of these drugs on postural hypotension occurring during tilt.

PATIENTS AND METHODS

This study was performed in 4 male and 3 female patients with MSA. Their age ranged from 55 to 75 years. All had progressive autonomic failure characterized by low levels of plasma norepinephrine, a blocked response to Valsalva's manoeuvre and marked postural hypotension and, in addition, had the central neurological features of multiple system atrophy (Shy and Drager, 1960). The control group represented 6 normal subjects previously described (Lightman and Forsling, 1980*a*). All control subjects and 4 of the patients with MSA had received no medication for at least one month before these studies (of the remaining 3 subjects with MSA, all were taking 9 α-fluorohydrocortisone at a dose of 0.1 to 0.2 mg/day and 2 were taking benzhexol at a dose of 8 and 15 mg/day). Subjects were deprived of fluid for 12 h overnight. Each was studied on three separate occasions, once with vehicle alone, once with naloxone and once with L-DOPA. The order of the studies was randomized except that L-DOPA studies were always performed last to vitiate any possible carry over effects from dopamine uptake into previously depleted dopaminergic neurons. At least 24 h elapsed between studies.

On each experimental day, a 21-guage cannula was inserted into one antecubital vein for infusions and a 19-guage cannula into the opposite antecubital vein for blood sampling. Subjects lay on a tilt-table without cushions or pillows. After 60 min in the horizontal position, a blood sample was drawn (time—40 min). Thereafter, an intravenous infusion was started at a rate of 0.47 ml/min containing either 0.15 M NaCl or naloxone (250 mg/l in 0.15 M NaCl) or L-DOPA (2.5 g/l in 0.15 M NaCl). These infusions were delivered for 85 min. No subjects experienced adverse effects during the infusions although one vomited after discontinuation of L-DOPA. These doses of naloxone and L-DOPA were shown previously to inhibit the rise of plasma AVP on tilt in normal subjects (Lightman and Forsling, 1980*a*, *b*). Our subjects were unaware which solution was being infused.

After 40 min of infusion, normal subjects were abruptly tilted head-up to 65 deg and patients with MSA were tilted until the systolic blood pressure fell by 30 mm Hg. The degree of tilt necessary for this effect had been determined the previous day. Each subject was tilted to exactly the same degree in all three studies and remained tilted until the end of the experiment 90 min later. No patients suffered syncope with this degree of tilt. Blood was drawn at time zero immediately after tilting and 45 and 90 min after the beginning of tilt for determination of plasma AVP concentrations. Pulse and blood pressure were recorded before tilt at −40 min and 0 min, and at 3, 45 and 90 min after tilt.

Mean blood pressure was calculated from the measurement of blood pressure made by a sphygmomanometer by adding one-third of the pulse pressure to the diastolic blood pressure (Korotkoff phase 5). Since the effects of L-DOPA and naloxone on blood pressure in patients with MSA were unknown, we elected to make the study 'single-blind' so that the investigator could intervene appropriately if required.

A two-tailed student t-test was used for within-patient comparisons and a single-tailed t-test for between-group comparisons. The study was passed by St. Mary's Hospital Ethics Committee. Patients gave their full and informed consent.

RESULTS

Mean Blood Pressure and Heart Rate

The changes in mean blood pressure and heart rate are shown in fig. 1 and the Table. Mean blood pressure after head-up tilt invariably fell in patients with MSA, but in normal subjects it rose at three minutes and then returned to baseline. Heart rate after tilt rose moderately in the patients with MSA. This rise was not significantly different from the control group in spite of the marked fall in mean blood pressure in the patients. This indicates that the cardiovascular reflexes of the patients were severely impaired but not completely absent. Naloxone infusions did not alter the resting mean blood pressure of the normal subjects or the patients with MSA nor the changes produced by tilt when these were compared with saline alone. L-DOPA did lower the mean blood pressure of these patients, however, both when they were horizontal and tilted; the mean blood pressure was significantly lower with L-DOPA than during saline infusion both before tilt ($P < 0.01$), and after 3 min ($P < 0.05$) and 45 min ($P < 0.05$) of tilting. In contrast, L-DOPA had no significant effect on the mean blood pressure of the normal subjects. Neither drug affected the heart rate in the basal state, but 3 min after tilt there was a greater increment in heart rate in patients with MSA when studied during L-DOPA than during saline infusion ($P < 0.05$).

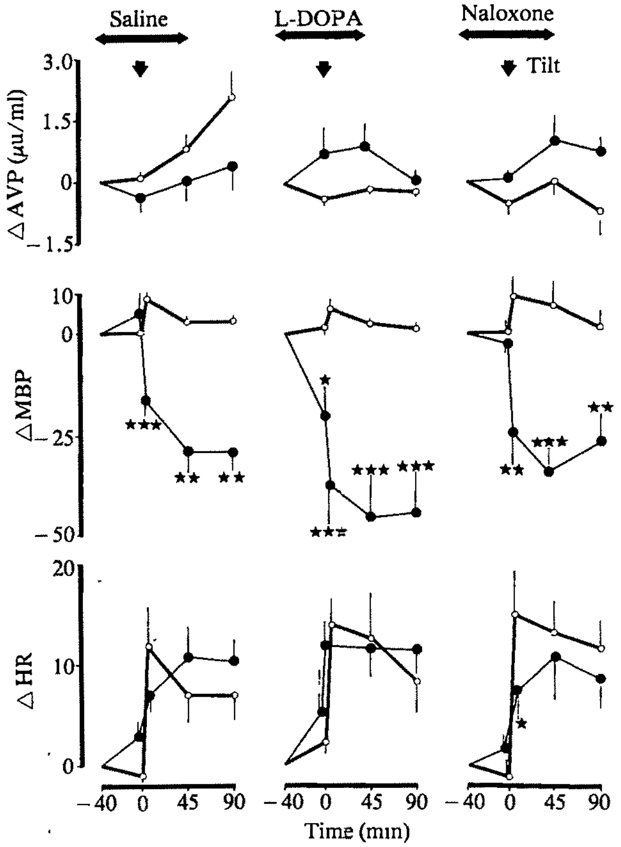

FIG. 1 Response of plasma arginine vasopressin (AVP) concentration, mean blood pressure (MBP) and heart rate (HR) to head-up tilt (at time 0 min) in control subjects (——o——) and patients with progressive autonomic failure (——●——). Intravenous infusions of either 0.15 M NaCl, naloxone 250 mg/l in 0.15 M NaCl or L-DOPA 2.5 g/l in 0.15 M NaCl were given at a rate of 0.47 ml/min from time −40 to +45 min. Values represent mean ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

TABLE BASELINE VALUES FOR HEART RATE, MEAN BLOOD PRESSURE AND ARGININE VASOPRESSIN

	Controls	*MSA*	P *value*
Heart rate (beats/min)			
Saline	69 ± 3.6	71 ± 2.0	n.s
Naloxone	64 ± 2.4	71 ± 3 0	< 0.05
L-DOPA	68 ± 10	66 ± 2.0	n.s.
Mean blood pressure (mm Hg)			
Saline	92 ± 2.3	112 ± 6.0	< 0.02
Naloxone	91 ± 3.1	114 ± 7.0	< 0.01
L-DOPA	90 ± 6.0	116 ± 12.0	n.s
Plasma arginine vasopressin (mU/l)			
Saline	0.68 ± 0.19	1.64 ± 0.64	n.s.
Naloxone	1.10 ± 0.31	1.04 ± 0.37	n.s.
L-DOPA	0.94 ± 0.17	1.34 ± 0.36	n.s.

Mean (± SEM) values recorded after 60 min in the horizontal position and just prior to the start of the infusions (time −40 min) in control subjects (n = 6) and patients with MSA (n = 7).

Plasma AVP Levels

The AVP levels are shown in fig. 1 and the Table. There was a rise in AVP after tilt in normal subjects that was statistically significant at 45 min ($P < 0.05$) and at 90 min ($P < 0.05$). This rise in AVP was abolished in the normal subjects by both L-DOPA and naloxone infusions, as reported previously (Lightman and Forsling, 1980*a*, *b*). In contrast, there was no significant rise in AVP levels above basal values after tilt in the patients with MSA at any time. Infusion of L-DOPA and naloxone both resulted in a small statistically insignificant increase in the AVP response to tilt, which was the opposite response to that seen in our control subjects.

DISCUSSION

Blood Pressure Response to L-DOPA and Naloxone

We showed previously that acute intravenous infusions of L-DOPA did not alter either the mean blood pressure or the heart rate of normal subjects during head-up tilt (Lightman and Forsling, 1980*a*). In the present study, however, we found that L-DOPA reduced the mean blood pressure of patients with MSA while they were horizontal and exaggerated the fall in mean blood pressure that occurred during tilt. This hypotensive effect of acute L-DOPA administration to patients with MSA confirms previous reports (Steiner *et al.*, 1974; Corder *et al.*, 1977) and is in contrast to the effect in chronic studies where some alleviation of orthostatic hypotension has been recorded (Maier, 1972; Aminoff *et al.*, 1973; Steiner *et al.*, 1974; Corder *et al.*, 1977). The explanation for the acute hypotensive response to L-DOPA is not clear. L-DOPA has both a central depressor action associated with a reduction in sympathetic nerve traffic and a pressor action probably due to peripheral dopamine formation (Henning and Rubenson, 1970; Watanabe *et al.*, 1970). Patients with MSA are supersensitive to the pressor effects of infused dopamine (Wilcox, Aminoff, Kurtz and Slater, 1974) and therefore the acute hypotensive response to L-DOPA is presumably mediated by a central action expressed *via* residual autonomic pathways. The present finding of worsening of postural hypotension during acute L-DOPA administration together with our previous finding of worsening of somatic motor defects during prolonged L-DOPA treatment (Aminoff *et al.*, 1973) and our unpublished experience of dramatic deterioration in some patients with MSA during withdrawal of L-DOPA lead us to recommend that this drug should not be prescribed for patients with MSA.

It has long been recognized that morphine can reduce blood pressure, particularly in the standing position, although the mechanism of action is complex (Bolme *et al.*, 1978; Lemaire *et al.*, 1978; Holaday and Faden, 1979; Rapoport *et al.*, 1980; Dashwood and Feldberg, 1980; Montastruc *et al.*, 1981). Of interest are the numerous reports that naloxone can reverse hypotension in haemorrhagic, endotoxic or spinal shock (Faden and Holaday, 1979, 1980; Reynolds *et al.*, 1980; Peters *et al.*, 1981; Faden *et al.*, 1981). It is clear from the present studies however, that naloxone given in a dose that is fully effective in blocking the postural rise in AVP in normal subjects does not alleviate the orthostatic hypotension of patients with MSA.

AVP Response to Tilt, L-DOPA and Naloxone

The plasma AVP level of normal subjects increases briskly during head-up tilt in response to decreased filling of the heart causing reduced pressure in the 'low pressure' cardiovascular system within the thorax (Davies *et al.*, 1976; Khokhar *et al.*, 1976; Lightman and Forsling, 1980*a*). The response was confirmed in the present studies where the AVP level increased progressively during tilting. In marked contrast, AVP levels in our patients with MSA failed to rise on tilt. The normal baseline levels of AVP in the patients with MSA found in the present study and the normal pituitary function reported previously (Wilcox *et al.*, 1975) suggest that the absence of a response to tilt is not due to pituitary damage. Moreover, it is most unlikely that the failure of AVP to rise on tilt in these patients was due to a failure to reduce the pressure in the low pressure cardiovascular system. Indeed, when patients with MSA are tilted head upwards, they have abnormal peripheral pooling of blood which leads to drastic reductions in venous return and cardiac filling (Hickman and Pryor, 1951; Page *et al.*, 1955) and therefore, presumably to an exaggerated reduction in pressure in the low pressure cardiovascular system. In addition, the mean blood pressure of the patients with MSA fell steeply during the tilting and this hypotensive response represents a considerable stimulus to AVP release (Abed *et al.*, 1982). Thus, the absence of a rise in AVP on tilting in patients with MSA indicates that they have a profound defect in the connections between the cardiovascular stretch receptors and the posterior pituitary gland.

In a previous study, Wilcox, Aminoff and Penn (1974) found that patients with

MSA failed to excrete a water load normally while they were standing. Moreover, during water deprivation the urine volume of patients with MSA increased during the night while they were recumbent and this was associated with a decrease in the excretion of antidiuretic activity in the urine measured by bioassay. The results of the present study using a specific immunoassay for AVP suggests that these postural fluctuations in excretion of antidiuretic activity may not represent AVP. Linden and colleagues have shown that a rise in atrial pressure can lead to a diuresis in dogs even after hypophysectomy, (Linden, 1979; Kappogoda *et al.*, 1979). Bioassay of the plasma of these dogs during decreased atrial pressure shows release of a substance that is distinct from AVP. Regardless of the cause for the abnormal control of urinary concentration in patients with MSA, it is clear from the present studies that these patients have a profoundly impaired ability to release AVP on head-up tilting.

Dopamine and opiates may alter the vasopressin response to tilt at several sites. At the level of the posterior pituitary gland itself, both dopamine and opiates directly inhibit AVP release (Lightman *et al.*, 1982), whilst at the level of the arcuate nucleus of the hypothalamus opiates stimulate AVP release (Lightman *et al.*, 1981). In addition the nucleus of the tractus solitarius has a rich catecholamine innervation (Dahlström and Fuxe, 1964, Palkovits and Jacobowitz, 1974), and a high concentration of opiate receptors (Atweh and Kuhar, 1977). All these three sites that have been implicated in posturally mediated AVP release are damaged in patients with MSA (Spokes *et al.*, 1979). In the present study we found that patients with MSA have a reversal of the normal response to both L-DOPA and naloxone. This alteration in neurological regulation of the AVP may contribute to the defect in tilt-stimulated AVP release that we found in patients with MSA.

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TRANSPORT OF OXYGEN TO THE BRAIN IN PATIENTS WITH ELEVATED HAEMATOCRIT VALUES BEFORE AND AFTER VENESECTION

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SUMMARY

Cerebral blood flow and oxygen transport to the brain have been studied in 20 patients with primary polycythaemia, before and after venesection. Cerebral blood flow rose by an average of 30 per cent ($P < 0.001$) when the mean haematocrit was reduced from 0.537 to 0.444. Whole blood viscosity fell predictably and the correlation coefficient between haematocrit and blood viscosity at a shear rate of $91\ s^{-1}$ was 0.926 ($P < 0.001$).

Mean arterial blood pressure, arterial PCO_2 and pH were not influenced by venesection. A small but significant overall rise in arterial PO_2 was observed but the arterial oxygen content fell with the reduction in haemoglobin concentration.

The product of cerebral blood flow and arterial oxygen content rose by an average of 8 per cent ($P < 0.001$) and this was considered physiologically significant because the position of the oxygen dissociation curve did not change. The increase in oxygen transport to the brain may serve to protect against ischaemic insult and other mechanisms whereby elevated haemotocrit might predispose to cerebral infarction are briefly discussed.

INTRODUCTION

Cerebral blood flow (CBF) is elevated in patients with anaemia (Scheinberg, 1951; Heyman *et al.*, 1952) and significantly reduced in patients with polycythaemia (Kety, 1949; O'Brien, 1971; Thomas *et al.*, 1977*a*, *b*). When the haematocrit is reduced by haemodilution, CBF increases in animals (Häggendal *et al.*, 1966), in normal man (Paulson *et al.*, 1973) and in patients with either polycythaemia rubra vera or high normal haematocrit values (Thomas *et al.*, *1977a*, *b*; Humphrey *et al.*, 1979). It has been suggested that the increase in blood flow which occurs when haematocrit is reduced reflects a homeostatic mechanism designed to maintain transport of oxygen to the brain in the face of the fall in arterial oxygen content (Olesen, 1974) and, during experimentally induced hypoxia, the increase in flow serves to ensure that as the arterial oxygen content falls, the product of CBF and arterial oxygen content remains constant (Jones *et al.*, 1981).

The delivery of oxygen to the brain depends not only on blood flow and arterial oxygen content, but also on the partial pressure gradient of oxygen across the capillary wall and the position of the oxygen dissociation curve. The importance of the latter in determining CBF has been demonstrated by a recent study which investigated CBF in patients with polycythaemia secondary to the presence of a haemoglobin variant characterized by high oxygen affinity (Wade *et al.*, 1980). CBF was elevated despite the increased arterial oxygen content, presumably because oxygen could not transfer readily to the tissues at the partial pressures encountered in the microcirculation. The conclusion was that delivery, rather than transport of oxygen to the brain, was the important factor determining CBF.

Both Thomas *et al.* (1977*a*, *b*) and Humphrey *et al.* (1979) reported that the increase in CBF which occurs on reducing the haemotocrit in patients with a high haematocrit, is well in excess of that predicted on the basis of the reduction in arterial oxygen content, which they estimated from the venous haemoglobin concentration by the nomogram of Shapiro (1973). Their studies also reported whole blood viscosity measurements performed *in vitro* before and after venesection, and they concluded that the increase in CBF was mainly due to the fall in blood viscosity which occurs when the haematocrit is reduced. Indeed, Humphrey *et al.* (1979) demonstrated a significant inverse relationship between CBF and whole blood viscosity and went on to speculate that haematocrit reduction might make more oxygen available to the brain.

Poiseuille (1842) defined the relationship governing flow, pressure and viscosity in round tubes, but he described the behaviour of Newtonian fluids (that is, fluids with a uniform viscosity at various rates of shear) in rigid tubes. Blood is a non-Newtonian fluid at low rates of shear and although the estimated rates of shear are high in the resistance part of the circulation (Whitmore, 1967), it is in these extremely small vessels where blood behaves in a highly anomalous fashion. The mechanics governing blood flow in the microcirculation will receive further attention in the Discussion; at this stage it should be emphasized that *in vitro* viscosity values, when performed on whole blood in relatively large bore viscometers, may have limited relevance to the analysis of blood flow in the circulation.

Thomas *et al.* (1977*b*) and Humphrey *et al.* (1979) implied that elevated haematocrit, and therefore blood viscosity when measured on whole blood in large bore viscometers, leads to a readjustment of the homeostatic mechanism which serves to couple CBF to cerebral oxygen utilization ($CMRO_2$). If this is true, then reducing the haematocrit should lead to more oxygen being transported to the brain in a form which is available to the tissues. Henriksen *et al.* (1981), however, failed to demonstrate a significant rise in oxygen carriage to the brain following acute haemodilution in 6 patients with neurological disease and marginally elevated haematocrit values. In the present study, CBF has been measured in 20 patients with elevated haematocrit, before and then several weeks after venesection. Ideally, we would have liked to measure $CMRO_2$ on each occasion, but this would have involved jugular bulb catheterization and was not considered justified. A compromise was to examine the oxygen transport mechanism by measuring the arterial blood gases, arterial oxygen content and the position of the oxygen dissociation curve before and after venesection. With these determinations, it was possible to see if haematocrit reduction leads to an increase in oxygen transport to the brain.

METHODS

CBF measurements were performed by the standard noninvasive procedure technique described by Thomas *et al.* (1979). This is a modification of the method described by Obrist *et al.* (1975) in which 5 to 8 mCi of ^{133}Xenon dissolved in 5 ml of normal saline were injected into a peripheral vein and the cerebral clearance was monitored by 6 extracranial sodium iodide crystals placed symmetrically around the head. End-tidal air concentrations of ^{133}Xenon were monitored by a seventh counter past which air was continuously drawn from the face mask, and values were taken to reflect arterial concentrations. The clearance curves were monitored for about 12 min and the flow value used in this paper refers to the slope of the first minute of the curve displayed semilogarithmically. A partition coefficient of 1.14 was used (based on the mean value calculated by Wyper *et al.*, 1976) and the flow values were corrected for the patient's haemoglobin level according to the method described by Veall and Mallett (1965).

Prior to the CBF measurement, a venous blood sample was taken from the anticubital fossa, without stasis, for haematocrit, blood viscosity and oxygen dissociation curve (ODC) measurements.

Haematocrit measurements were performed on blood anticoagulated with EDTA (1.5 mg/ml) using a microhaematocrit method and 10 min centrifugation. Blood, anticoagulated with lithium heparin, was used for the whole blood viscosity measurements and these were performed in a coaxial cylindrical viscometer (Contraves Low Shear Viscometer). Measurements were performed at 37° C and at a shear rate of 91 s^{-1}. The latter was chosen because it is near the limit of the apparatus and although rather less than the estimates of shear rate in the microcirculation, it is in the range at which blood behaves as a Newtonian fluid (Whitmore, 1968).

Oxygen dissociation curves were plotted on an Aminco Hem-O-Scan analyser. This apparatus exposes 1-2 μl of blood to increasing pressures of oxygen and measures the percentage oxyhaemoglobin of the sample spectrophotometrically. The sample is placed in a chamber maintained at 37° C, and the partial pressure of oxygen (PO_2) is monitored by a Clark electrode. The ODC is measured in the presence of 5.6 per cent carbon dioxide which serves to maintain the pH at 7.4. The position of the dissociation curve is reflected by the P_{50}, which is the PO_2 at which haemoglobin is half saturated with oxygen and this is the value given in the Results section.

At the end of the CBF study, a sample was taken from the radial artery into a heparinized glass syringe. The syringe contained a small washer to facilitate mixing. Filling took between 1 to 2 min and great care was taken to avoid introducing air into the sample. The sample was then capped and placed immediately in crushed ice. Blood gas analysis was performed on an ABL 1 Acid-Base analyser (Radiometer) and the arterial oxygen content was measured with a Lex O_2 Con Total O_2 Content analyser (Lexington Instruments). Both estimations were performed within 2 h of sampling, a delay which has been shown not to influence the results (Wade, 1981*b*).

One CBF measurement was carried out prior to venesection and the second measurement was performed at least five days after the last venesection. The venesection regime consisted of weekly sessions during which 300 to 450 ml of blood were taken and this was pursued for an average of eight weeks (range 3 to 13 weeks) until the haematocrit was within the desired range.

The patients acted as their own controls and a paired t-test was used for the statistical analysis of the results.

All patients gave informed consent and the study was approved by the Ethical Committee of St. Thomas' Hospital, London.

PATIENTS

Twenty patients, who were referred to the Department of Haematology at St Thomas' Hospital with an elevated haematocrit, form the basis of this study. Initial investigations were performed on 23 subjects but 2 patients defaulted during the course of venesection and the third underwent treatment for thyrotoxicosis before the repeat CBF measurement was undertaken. None of the subjects had been venesected in the past.

Details of the 20 patients are shown in Table 1. The haematological diagnosis was based on the criteria outlined by Wetherley-Mein and Pearson (1982). Six patients had polycythaemia rubra vera (PRV), 4 had idiopathic erythrocytosis (IE), while the remainder had apparent polycythaemia (AP). 'Apparent polycythaemia' refers to a condition in which the red cell mass is not elevated, but some combination of a definitely reduced or low normal plasma volume and a high normal red cell mass cause an elevation of haematocrit. Seven patients presented with symptoms referrable to the central nervous system, 4 of whom had suffered either a completed stroke or transient ischaemic attack (Cases 2, 6, 14 and 16) prior to the study. Only one of these subjects had residual signs, which consisted of a

TABLE 1 PRESENTATION AND HAEMATOLOGICAL DIAGNOSIS IN 20 PATIENTS WITH PRIMARY HIGH HAEMATOCRIT

Case	*Sex*	*Age (yrs)*	*RCM* (%)*	*PV* (%)*	*Haematological diagnosis***	*Presentation and treatment*
1	M	53	+18	+ 3	AP	L. ulnar nerve palsy
2	M	64	+34	+ 5	IE	Small brainstem infarct. Hypertension. Atenolol, Moduretic.
3	M	54	+27	−11	IE	Chest infection
4	M	51	+24	+ 3	AP	Routine blood count
5	M	73	+17	− 3	AP	Angina Glyceryl trinitrate.
6	M	60	+63	+ 8	PRV	One episode of transient diplopia
7	F	68	+37	− 7	IE	Dermatitis
8	F	59	+12	− 5	AP	Pruritis
9	M	55	− 7	−17	AP	Parkinson's disease. Hypothyroidism. Thryroxine, Sinemet.
10	M	52	+ 2	−13	AP	Multiple sclerosis
11	M	62	Not done		PRV	Intermittent claudication
12	M	47	+24	−11	AP	Hypertension. Propranolol, Bumetamide.
13	M	52	+17	−11	AP	Gastritis. Hypertension. Propranolol.
14	M	47	−19	−21	AP	Vertebrobasilar transient ischaemic attack. Aspirin.
15	M	59	+25	+ 4	PRV	Cutaneous infarction L toe. Busulphan, aspirin.
16	M	59	+31	+ 6	PRV	Hypertension. Stroke with residual weakness in L. arm. Hydroflumethiazide, debrisoquine sulphate.
17	F	50	+60	− 9	IE	Routine blood count. ?Thyrotoxicosis.
18	M	47	+20	−19	AP	Lethargy Gastritis.
19	F	62	+91	+ 1	PRV	Duodenal ulcer. Antacids.
20	F	64	+60	+ 7	PRV	Routine blood count

*RCM = red cells mass. PV = plasma volume, both expressed as percentage increase or decrease above or below the predicted normal value (Nadler *et al.*, 1962). **AP = apparent polycythaemia. IE = idiopathic erythocytosis, PRV = polycythaemia rubra vera.

weak left arm, at the time of study (Case 16). Of the remaining 3 patients with neurological symptoms, one had a left ulnar nerve palsy (Case 1), one had Parkinson's disease (Case 9) for which he was receiving Sinemet, and the third had a partial lumbar cord lesion which was ascribed to multiple sclerosis (Case 10). The drug regimes, which are shown in Table 1, were unaltered during the period of study. One patient (Case 9) had hypothyroidism diagnosed three years prior to referral and was euthyroid at the time of study on thyroxine 0.15 mg daily. In another patient (Case 17), thyrotoxicosis was suspected on clinical grounds but the results of thyroid function tests were equivocal and she was not on treatment.

Fourteen of the 20 patients were smokers and no attempt was made to change their smoking habits during the period of study. The second measurements of CBF, venous P_{50} and arterial oxygen content were performed at the same time of day as the first and it was assumed that the percentage carboxyhaemoglobin was similar on both occasions although this was not actually measured.

RESULTS

Table 2 gives details of the mean arterial blood pressure, haematocrit and CBF in the 20 patients, before (*b*) and after (*a*) venesection. The mean arterial blood pressure (MABP) was not significantly influenced by venesection. Mean haematocrit

TABLE 2. MEAN ARTERIAL BLOOD PRESSURE (MABP), HAEMATOCRIT, WHOLE BLOOD VISCOSITY AND CEREBRAL BLOOD FLOW (CBF) IN PATIENTS BEFORE (*b*) AND AFTER (*a*) VENESECTION

	MABP (mm Hg)		*Haematocrit*		*Whole blood viscosity ($mNsm^{-2}$) at shear rate of 91 s^{-1}*		*CBF (ml/100 g/min)*	
Case	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)
1	96	109	0.504	0.456	5.73	5.23	32.9	38.4
2	110	105	0.578	0.401	6.73	3.87	26.7	42.7
3	103	109	0.542	0.482	6.77	5.52	31.8	39.9
4	141	132	0.544	0.468	6.24	4.80	31.1	36.9
5	111	117	0.530	0.440	6.66	5.01	23.9	33.5
6	115	106	0.582	0.467	6.65	4.66	31.1	45.1
7	98	104	0.497	0.427	5.62	4.33	32.3	40.7
8	116	107	0.492	0.419	4.96	4.50	35.3	48.6
9	125	127	0.518	0.446	6.09	5.30	31.0	33.7
10	107	104	0.524	0.424	5.87	4.58	32.2	41.5
11	112	109	0.521	0.368	6.87	4.16	33.4	47.9
12	124	111	0.528	0.459	6.13	5.02	28.4	42.1
13	123	109	0.557	0.456	7.38	5.44	32.1	45.3
14	103	103	0.499	0.455	6.02	4.68	30.6	34.7
15	140	115	0.593	0.442	7.45	4.66	26.2	36.6
16	124	116	0.528	0.460	6.30	5.47	26.6	34.9
17	106	102	0.541	0.433	6.48	4.16	50.8	61.1
18	116	105	0.509	0.446	5.30	4.80	27.2	33.5
19	101	96	0.616	0.474	8.82	5.44	36.9	46.0
20	109	113	0.537	0.464	6.02	5.16	30.7	40.8
Mean	114	110	0.537	0.444	6.40	4.84	31.6	41.2
SD	13	8	0.034	0.027	0.85	0.48	5.5	6.7
P	n.s		< 0.001		< 0.001		< 0.001	

was reduced from 0.537 (SD 0.034) to 0.444 (SD 0.027, $P < 0.001$) and this was associated with an increase in mean CBF of 30 per cent from 31.6 (SD 5.5) ml/100 g/min prior to venesection to a mean value of 41.2 (SD 6.7) ml/100g/min after venesection ($P < 0.001$). Venesection led to a consistent and significant reduction in whole blood viscosity at the shear rate of 91 s^{-1}. The mean value before venesection was 6.40 (SD 0.85) $mNsm^{-2}$ and following venesection the equivalent value was 4.84 (SD 0.48) $mNsm^{-2}$ ($P < 0.001$). Individual results are included in Table 2. When haematocrit was plotted against blood viscosity a correlation coefficient of 0.926 was obtained ($P < 0.001$).

Table 3 documents the individual changes in PaO_2, $PaCO_2$, pH, P_{50}, arterial oxygen content and the product of CBF and arterial oxygen content, referred to as oxygen transport in ml/100 g/min.

The mean arterial oxygen tension (PaO_2) was 69 (SD 8) mm Hg prior to venesection and rose significantly ($P < 0.005$) to a mean value of 74 (SD 7) mm Hg

TABLE 3. BLOOD GASES, P_{50}, ARTERIAL OXYGEN CONTENT AND OXYGEN TRANSPORT (CBF × ARTERIAL OXYGEN CONTENT) IN PATIENTS BEFORE (*b*) AND AFTER (*a*) VENESECTION

	PaO_2 (mm Hg)		*$PaCO_2$ (mm Hg)*		*pH*		*P_{50} (mm Hg)*		*O_2 content (ml/100 ml)*		*O_2 transport (ml/100 g/min)*	
Case	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)
1	70	78	37	39	7.42	7.43	29.4	28.5	20.0	18.3	6.58	7.03
2	64	75	38	41	7.43	7.42	30.1	29.6	22.0	16.9	5.87	7.22
3	68	69	36	35	7.44	7.42	26.3	26.4	20.3	18.9	6.45	7.54
4	67	73	38	40	7.41	7.39	28.6	27.0	20.0	16.8	6.22	6.20
5	60	71	32	33	7.44	7.43	30.0	29.2	21.7	17.3	5.18	5.79
6	57	72	34	41	7.44	7.40	28.1	29.0	19.2	16.4	5.97	7.40
7	67	74	40	39	7.42	7.40	30.5	28.9	19.0	15.5	6.14	6.30
8	61	66	37	36	7.40	7.45	29.6	29.0	18.8	15.8	6.64	7.68
9	60	57	35	35	7.44	7.44	26.9	27.5	19.7	17.7	6.11	5.98
10	72	71	36	35	7.43	7.44	27.9	27.7	20.8	18.1	6.68	7.51
11	74	88	41	38	7.38	7.41	30.0	26.8	21.0	14.7	7.01	7.04
12	70	79	37	40	7.42	7.40	27.7	27.6	20.6	18.2	5.95	7.66
13	66	67	37	34	7.43	7.42	27.7	26.2	22.8	18.3	7.32	8.29
14	73	82	34	33	7.44	7.45	27.6	27.5	20.7	18.0	6.33	6.25
15	68	67	37	40	7.41	7.38	27.4	28.9	21.9	15.9	5.74	5.82
16	66	75	39	39	7.44	7.45	25.2	26.2	21.4	18.2	5.69	6.63
17	67	74	40	40	7.41	7.40	24.6	26.1	19.2	15.5	9.75	9.74
18	91	86	36	36	7.43	7.44	28.9	26.9	20.2	18.6	5.49	6.23
19	71	75	38	39	7.42	7.42	27.6	27.7	22.4	17.1	8.26	7.87
20	79	77	36	37	7.41	7.40	28.7	26.8	20.6	17.3	6.32	7.06
Mean	69	74	37	37	7.42	7.42	28.1	27.7	20.6	17.2	6.48	7.03
SD	8	7	2	3	0.02	0.02	1.6	1.1	1.2	1.2	1.03	0.94
P	< 0.005		n.s.		n.s		n.s.		< 0.001		< 0.001	

following venesection. The mean prevenesection arterial carbon dioxide tension ($PaCO_2$) was 37 (SD 2) mm Hg and this was not significantly affected by venesection. Individual changes in $PaCO_2$ were small (3 mm Hg or less) in all cases, with the exception of Case 6 in whom it rose from 34 to 41 mm Hg and was associated with an increase in PaO_2 from 57 to 72 mm Hg. The mean pH before haematocrit reduction was 7.42 (SD 0.02) and the value after venesection was identical. The initial mean P_{50} was 28.1 (SD 1.6) mm Hg and did not differ significantly from the normal for our laboratory which is 27.7 (SD 1.3) mm Hg, based on 25 observations. The postvenesection mean P_{50} was 27.7 (SD 1.1) mm Hg and this did not differ significantly from the prevenesection value.

Venesection was associated with a mean drop in arterial oxygen content of 17 per cent from 20.6 (SD 1.2) ml/100 ml to 17.2 (SD 1.2) ml/100 ml ($P < 0.001$) (Table 3). The mean cerebral oxygen transport, derived from the product of CBF and arterial oxygen content, was 6.48 (SD 1.03) ml/100 g/min prior to venesection and 7.03 (SD 0.94) ml/100 g/min following venesection. This represents an overall increase of 8 per cent, which was significant ($P < 0.001$), paired t-test.

Appreciable increases in cerebral oxygen transport (7 per cent or greater) occurred in 12 patients (Cases 1, 2, 3, 5, 6, 8, 10, 12, 13, 16, 18 and 20, Table 3) and in 8 patients (Cases 4, 7, 9, 11, 14, 15 and 19, Table 3) oxygen transport remained constant. Statistical analysis was undertaken in an attempt to differentiate the 12 patients in whom cerebral oxygen transport went up from the 8 in whom it did not. Significant differences in the degree of haematocrit reduction, or the change in blood viscosity did not emerge, and other factors, such as MABP and arterial gas tensions were comparable between the two groups. An attempt at clinical differentiation on the basis of age, haematological diagnosis and the presence or absence of neurological disease was also unsuccessful.

DISCUSSION

The present study has confirmed that treatment designed to lower the haematocrit in patients with primary polycythaemia leads to a significant increase in CBF. Whole blood viscosity, when measured *in vitro* in a large bore viscometer, falls predictably as the haematocrit is reduced and the arterial oxygen content also drops as the haemoglobin concentration is lowered. Venesection does not, however, influence the position of the oxygen dissociation curve under the test conditions used in this study, and since arterial PCO_2 and pH remain relatively constant, haematocrit reduction will not affect the ease with which bound oxygen diffuses into the cerebral tissue.

It has been shown that the increase in CBF more than compensates for the fall in arterial oxygen content because the product of CBF and arterial oxygen content increases significantly following venesection. More oxygen is therefore transported to the brain and it is in a form that is available to the tissues. If we assume that $CMRO_2$ remains constant, then the ratio of CBF to $CMRO_2$ is increased by venesection. This may occur because the autoregulatory mechanism which matches CBF to $CMRO_2$ is less efficient when the blood viscosity is elevated, but before discussing this further it is worth commenting on the blood gas results obtained before and after venesection.

$PaCO_2$ values were within the accepted normal range and were not influenced by venesection, but the mean PaO_2 was low prior to venesection and this merits further consideration. The samples were analysed within 2 h and previous work has shown that a delay in this duration does not add a systematic error provided that the samples are kept at 0° C (Wade, 1981*b*). There is evidence which suggests that PaO_2 is influenced by the posture of the subject at the time of study and all subjects had been supine for at least 20 min by the time of sampling. Leblanc *et al.* (1970) have demonstrated that significant ventilation/perfusion mismatching occurs in normal middle aged individuals when they assume the supine position, and this phenomenon is more pronounced in patients with either apparent polycythaemia or idiopathic erythrocytosis (Ward *et al.*, 1968). The present study suggests that elevated haematocrit may itself contribute to this because mean PaO_2 rose significantly following venesection. However, it is quite possible that occult hypoxaemia was responsible for the erythrocytosis in some patients diagnosed as having apparent polycythaemia, an explanation which remains speculative in the absence of a reliable erythropoietin assay. The increase in PaO_2 meant that the fall in arterial oxygen content following venesection was less than that predicted on the basis of the reduction in haemoglobin concentration alone.

The significance of *in vitro* whole blood viscosity measurements may be limited and the provisos mentioned in the Introduction warrant further discussion before returning to the relationship between CBF and blood viscosity. In the larger arteries, blood flow is influenced both by inertia and viscosity, whereas in the microcirculation it is dominated by viscous forces. The main pressure drop (that is, energy loss) in the circulation occurs within the microcirculation, defined here as those vessels having a diameter of less than 100 μm (Caro *et al.*, 1978). This definition includes the arterioles, capillaries and venules, and it is in these vessels that flow rates are essentially determined by local pressure gradients and viscous forces.

Poiseuille's law states that

$$\text{rate of flow} = \frac{\Delta P}{L} \times \frac{r^4}{\eta} \times \frac{\pi}{8},$$

where ΔP is the pressure gradient, r is the radius of the tube, L the length of the tube, and η the viscosity of the fluid. The law, however, applies only to Newtonian fluids in rigid tubes. Blood behaves as a Newtonian fluid above a certain shear rate (approximately 100 s^{-1}, Whitmore, 1968) and estimations of the wall shear rates in the microcirculation suggest that the value may be high enough to ensure Newtonian behaviour (Whitmore, 1967; Dintenfass, 1971, p. 117). However, the 'tubes' of the microcirculation are not rigid and a previous study, which examined the cerebrovascular response to changes in $PaCO_2$, has shown that the microvessels are not maximally dilated even when flow is reduced and the viscosity elevated (Wade, 1981*a*). A further criticism of the direct application of Poiseuille's law to the flow dynamics of the microcirculation is that, under these conditions, blood behaves as a particulate fluid and displays anomalous behaviour. *In vitro* experimentation has demonstrated that the apparent viscosity of blood falls in tubes of less than 300 μm (Fåhræus and Lindqvist, 1931) and continues to do so until the tube size is of the order of 6 μm or less, at which point the diameter of the red cells exceeds that of the vessel (Dintenfass, 1971). The apparent viscosity then rises sharply and will depend on the energy required to deform the red cells. Thus, measurements of whole blood viscosity, performed *in vitro* on relatively large specimens at relatively low rates of shear, may significantly overestimate the role of haematocrit in determining the flow properties of blood in that part of the circulation where viscous energy losses are greatest. The present study has shown that a profound drop in whole blood viscosity is associated with a small, albeit significant, increase in oxygen transport to the brain.

There is no doubt that patients with primary polycythaemia suffer an increased incidence of vascular occlusive episodes, with the cerebral circulation most notably at risk (Chievitz and Thiede, 1962; Barabas *et al.*, 1973; Pearson and Wetherley-Mein, 1978). It seems the critical factor underlying this relationship is the height of the haematocrit with other factors, such as an increased platelet count, assuming secondary importance (Pearson and Wetherley-Mein, 1978). Indeed the haemoglobin value has been identified as an important risk factor for cerebral infarction in the normal population (Kannel, *et al.*, 1972), an observation confirmed by the pathological study of Tohgi *et al.* (1978). The height of the haematocrit may also have a bearing on the size of the infarct as has been demonstrated in both animals and man (Harrison *et al.*, 1981; Pollock *et al.*, 1982).

It is tempting to ascribe the association between elevated haematocrit and the increased incidence of cerebral infarction to abnormal blood fluidity. Our data have shown that haematocrit reduction leads to an increase in oxygen transport in some patients and this may protect against ischaemic insult but, for reasons already discussed, the *in vitro* demonstration of abnormal blood viscosity may reflect a potential rather than actual property of the blood in the normal circulation. This potential property may assume clinical significance, however, when superimposed on a diseased vascular bed in which the vasodilatory reserve has been exhausted. Such a situation might exist around an early cerebral infarct, and if the vessels are maximally dilated then flow rates will depend solely on local pressure gradients and viscous forces, and might be significantly improved by haematocrit reduction. Another physical property of blood, influenced by the haematocrit level, is the 'yield stress', a term which refers to the minimal force required to start blood flowing once it has been stationary. The magnitude of the yield stress depends on the height of the haematocrit (Merrill *et al.*, 1963) and elevated haematocrit may therefore prevent effective restoration of blood flow after transient cessation. Finally, whatever the mechanism underlying the inverse relationship between CBF and haematocrit, low flow may itself predispose to thrombus formation at sites of vessel disease. There now seems sufficient theoretical and empirical evidence to warrant a clinical trial into the role of haemodilution in the management of patients who present with cerebrovascular disease and are found to have marginally elevated haematocrit values.

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NOTICES OF RECENT PUBLICATIONS

Essentials of Neurology. Fifth Edition. By Sir John Walton. 1982. Pp. 488. London: Pitman. Price £10.95.

Essential Neurology. Second Edition. W. Pryse-Phillips and T. J. Murray. 1982. Pp. 714 New York. Medical Examination Publishing. Price $32.50.

Neurology, according to most undergraduates and many postgraduate students, is difficult. Conditions with eponymous titles abound and are manifest by complex constellations of neurological signs. Their teachers may have unwittingly encouraged this view by expressing enthusiasm over rare diagnoses and delighting in the minutiae of the examination. Diagnoses appear as though from the conjurer's hat.

Both these books are a response to the consumer's demand for a simple text that will introduce the relevant anatomy and physiology, explain the fundamentals of good clinical examination and present the problems of differential diagnosis clearly. The two texts follow this format but there are significant differences. Walton's book is more in the tradition of the large textbook and has scaled-down thumbnail sketches of a wide range of neurological conditions; the Canadian book reads more like a tutor, spending more time, for example, on the interpretation of signs. The Canadian text has the advantage of being physically bigger so that its figures are more numerous, and larger and clearer to read. There is space for a more relaxed prose style compared to Walton's tighter writing. Pryse-Phillips and Murray write attractively in the second person encouraging the student to look for this and to beware of that. It is refreshing, too, to see their statement that serial observation of the patient is a form of neurological investigation.

There are minor errors and omissions in both texts. For example, Pryse-Phillips and Murray, in discussing the difference between vertigo of central and peripheral cause, seem to confuse the features of positional vertigo and in the section on strokes imply that all lacunes are haemorrhages. Walton's text seems to leave some ambiguities in the distinction between papilloedema and 'papillitis', and it lacks perspective when describing different kinds of dysphasia. These are all small points that could be ironed out next time.

This is the fifth edition of the Pitman publication and the formula has obviously been a success. The transatlantic *Essential Neurology* also deserves success and may be preferred by undergraduates who will find it more 'consumer friendly', though it costs nearly twice as much. Postgraduates looking to revise the subject will find more in Walton's little book.

M. J. G. HARRISON

Neonatal Neurology. Edited by Mary Coleman. 1981. Pp. 417. Baltimore: University Park Press. Price $65.00.

Dr Coleman and her ten contributors have produced a very impressive and attractive looking book with liberal illustrations. Unfortunately, the topics covered vary considerably in length, in depth, in quality and in their practical usefulness, and it is doubtful that this book will find appeal either to the expert in the field or the trainee. A number of sections are extremely comprehensively done, such as the 70-page review of neuroradiology with lavish illustrations of radiographs, CT scans, arteriograms and also radionuclide scans, the 20-page review of chromosome disorders and the

20-page review of genetic metabolic disorders likely to give neurological problems in the neonate. In contrast, some of the important neurological problems in the newborn, such as hydrocephalus and meningomyelocoele, are dealt with very superficially and dismissed in a few short pages. In the section on the neurological examination of the neonate a large part is devoted to physical measurements of the newborn infant, including a number of standard charts for height, weight and head circumference, while the neurological examination itself gives very little practical detail and comprises mainly a review of the literature with a long list of references and very little critical comment on what contribution, if any, many of these authors have made. The chapter on interpretation of the neurological examination tabulates long lists of possible causes for various common clinical symptoms and signs but makes no effort to separate the common and important ones from the very rare and unlikely syndromes. The book contains an excellent review of prenatal factors likely to affect the nervous system, including maternal infection, other diseases, medication and nutrition. There is also a comprehensive review of convulsions in the newborn, but I found the 'immediate management' somewhat unconventional and it would certainly not be common practice in Britain to give an intravenous infusion of hyperosmolar dextrose.

As a reference source, Volpe's *Neurology of the Newborn* provides a broader and more balanced coverage of this important and growing field.

V. Dubowitz

Progress in Perinatal Neurology. Volume 1. Edited by Rowena Korobkin and Christian Guilleminault. 1981. Pp. 238. Baltimore: Williams & Wilkins. Price $42.00.

This is a collection of ten contributions by well-known authors on aspects of the neurology of the newborn infant. It provides a useful source of information on the particular topics under review, although the contents of many of them reflect mainly the personal views of the authors rather than giving a comprehensive and balanced review of the literature. The first contribution (Dargassies) covers the normal evolution of neurological signs in the newborn infant from prematurity to full term and lists some of the abnormalities that may occur. Subsequent sections deal with the effects of birth injury on brain dysfunction in the full-term infant (Amiel-Tison) and the prognosis for survivors of perinatal intraventricular haemorrhage (Korobkin). There is also a section devoted to intraventricular haemorrhage in the premature neonate, seen through the eyes of the pathologist (Larroche). Other topics covered include the nutrition of the developing brain (Pratt), the role of lactic acid accumulation as a cause of brain oedema and cerebral necrosis after oxygen deprivation (Myers) and a review of other problems in the neonatal period including neuromuscular disorders (Sarnat), neonatal seizures (Dennis), sleep states (Guilleminault and Souquet) and development of respiratory control (Ariagno)

This is a rapidly growing field and this type of book which brings together reviews of important topics in the field is a welcome addition to one's reference library

V. Dubowitz

The Autonomic Nervous System. An Introduction to Basic and Clinical Concepts. Third Edition. By Otto Appenzeller. 1982. Pp 524. Amsterdam: Elsevier Biomedical Press. Price Dfl. 260.00.

In the past twenty years clinical knowledge of autonomic function has burgeoned and Dr Appenzeller's earlier editions have done much to accelerate the rate of progress. This third edition is much enlarged by the provision of new material about catecholamines, the newer neuropeptides and receptor function, and in particular, reference to studies of sympathetic receptors marked by ligand binding techniques. For example, we must now refine the concept of alpha receptors into alpha$_1$ receptors which include the postsynaptic receptors of smooth muscle and the alpha$_2$ receptors some of which are presynaptic receptors which act as an inhibitory alpha receptor feedback control. Receptors may be 'up' and 'down' regulated by their exposure to levels of circulating agonist, and sympathomimetic and blocking drugs have to be reclassified according to their actions on each subtype if the appropriate clinical benefits are to be obtained in autonomic disorders. Curiously, for reasons not understood, there are alpha receptors on platelets and beta receptors on lymphocytes whose presence and accessibility to ligand binding studies has provided a new research method of estimating overall sympathetic receptor function in conjunction with plasma catecholamine assays.

This new edition provides a valuable review of recent progress in autonomic anatomy and physiology. Among the many areas of particular interest are the review of renal and baroreceptor defects in hypertension, the ultimate causes of which seem to be as elusive as ever, and also the little understood areas of operant conditioning and feedback. Also new material is included on trophic disturbances, respiratory disturbances and sleep apnoea. The management of chronic pain receives new attention, though the useful recent technique of sympathetic block using intravenous guanethidine is not included. He does not neglect a personal interest in temperature regulation during marathon running which has yielded valuable information on the responses of man at extreme limits of endurance. Dr Appenzeller is to be praised for his breadth of coverage and this edition will again provide a very valuable reference for the clinician who increasingly encounters problems of autonomic function in clinical practice.

ROGER BANNISTER

Therapy for Neurologic Disorders. Edited by W. C. Wiederholt. 1982. Pp. 437. Chichester: John Wiley. Price £35.00.

This book is a collection of thirteen chapters on separate topics relevant to therapy for neurological disorders each by a different author. The order of their presentation seems to have been a somewhat random process; the information on individual drugs is meagre, and some important general topics, such as the blood-brain barrier, are not addressed. Nevertheless, most of the common therapeutic approaches to neurological disorders are covered, though sometimes in the form of a rather personal view of the author. Perhaps this is unavoidable in such a multiauthor work. The chapters on Metabolic Encephalopathies, Dementia, and Degenerative and Hereditary Disorders, are comprehensive and well written, and throughout this book the generous use of tables is helpful.

This book is well produced. Most readers will certainly find something of interest. Several books on therapy for neurological disorders are now available, a remarkable achievement in a field that was considered therapeutically barren for so long. The drawbacks of any therapeutic work are well summarized by the editor; the subject is moving so rapidly in some areas that 'regrettably, but unavoidably, when this book reaches its readers, some therapies may already be outdated'. The rapid spawning of books on neurological therapeutics indicates that in spite of these limitations, many neurologists are finding such publications worthwhile.

DONALD B. CALNE

Computed Emission Tomography. Edited by P J. Ell and B. L. Holman. 1982. Pp. 546. Oxford University Press. Price £50.00.

This review considers *Computed Emission Tomography* from the viewpoint of readers of *Brain* many of whom are likely to have an interest in, but no specialized knowledge of, emission tomography. The book will undoubtedly prove useful to workers within the field, but the back cover also claims that many others involved in medical research or clinical medicine will 'derive useful information from many topics covered in this volume'. Whether this is true for neurologists and neuroscientists forms the subject of this particular review.

There are two ways of approaching emission computed tomography. The first is to consider it as a rival to x-ray transmission computed tomography in the realm of diagnostic imaging. The alternative is to see it as a unique method of measuring, *in vivo*, tissue function in health and disease. Both aspects are covered in this multiauthor book. The topics covered include the theory and problems inherent in emission tomography, synthesis of radiolabelled tracers, modelling of the tissue distribution of tracers, and the application of emission tomography to clinical research and diagnosis. The greater proportion of the chapters on application are devoted to the brain. Positron and single photon emission tomography of the heart and single photon emission tomography of the liver, spleen and lungs are also considered in other chapters.

The layout of the book has been so arranged that positron emission tomography (PET) has been firmly separated from single photon emission tomography (SPET). The result is two books between the covers of one. As PET and SPET are directed towards a common goal, this division will undoubtedly puzzle the nonspecialist reader This could have been avoided if there had been a chapter devoted to the basic theory of PET and SPET, their similarities and dissimilarities, advantages and disadvantages. As it is, there is only one brief paragraph in the chapter on PET instrumentation dealing with the fundamental concept behind data collection in PET, namely, annihilation coincidence detection. Three chapters on SPET cover instruments that are available, and the details of problems associated with attenuation and noise: yet it will take an alert reader, previously unaware of the fact, to register that the main advantage of PET over SPET is the relative ease of correcting for attenuation with the former. When considering the four chapters on the collection and reconstruction of emission data overall, it becomes apparent that they assume a considerable knowledge of the more basic underlying concepts. The nonspecialist reader will search in vain for the chapter that links those presented into a more coherent whole.

The same problem underlies the reviews of radiolabelled tracers. Those compounds available for use with PET are dealt with in one chapter which is almost pure radiochemistry A long list of positron-emitting compounds potentially useful for *in vivo* receptor studies (mainly neuroreceptors) is presented—with no hint of the unresolved problems that lie behind their use to demonstrate meaningfully the distribution and concentration of specific neuroreceptors within the brain. The chapter on receptor-specific radiopharmaceuticals designed for use with SPET does, however, consider these problems briefly. The review of tracers suitable for studying many aspects of metabolism with SPET is another contribution strongly biased towards presenting details of synthesis, but concludes that of the many tracers discussed only a very few have been (ever will be?) used in human studies. Once again the individual authors have produced excellent reviews, but the sum of their contributions is a very incomplete jigsaw. As the study of tissue function *in vivo* relies on well-validated tracer techniques a review of the principles and problems of tracer kinetics employed in understanding physiological processes of varying complexity would have been particularly useful, and would have helped put the other chapters in context.

Detailed consideration of the tracer modelling for the few radioactive compounds that have proved useful in practice is largely left to the chapters on the application of emission tomography. Five chapters cover emission tomography of the brain. One deals with the use of SPET in diagnostic imaging. This is a review of the success of this technique at localizing focal cerebral lesions and subdural collections, and a direct comparison is made with x-ray CT scanning. The overall conclusion that SPET is very good at diagnosing/confirming some cerebral conditions is well made, although it is unlikely to divert neurologists and neurosurgeons from their justifiable enthusiasm and reliance on x-ray CT scanning in diagnosis and patient management. The other four are concerned with measurement of regional cerebral function. One chapter in the PET section is ambitiously entitled 'The Brain', but then only considers aspects of regional cerebral glucose metabolism under varying physiological and pathophysiological conditions. However, it is a good general review of the current use of PET and the fluorine-18 deoxyglucose techniques in cerebral studies. It is followed by a useful chapter on the early results that have been achieved with the oxygen-15 technique to measure regional cerebral blood flow and oxygen utilization. In comparison, the two SPET chapters on regional cerebral blood flow studies are disappointing This is partly because they have not yet generated the interesting results that have come from the two dimensional studies with static detectors and the xenon-133 technique, and the results presented in this book are largely in the form of anecdotes.

In conclusion, the editors have gathered together the independently written chapters from their contributors and have been left with a series of essays, not a book. This inevitably reduces its value to the nonspecialist reader, who will have to do some carefully planned reading elsewhere to get the full benefit of the largely excellent individual chapters. Neurologists will gain most from the chapters on application, especially if they are open to persuasion about the potential future of studies that examine normal and abnormal human regional cerebral function. They might like to end with the final chapter of the PET section, which contains an honest assessment of the, as yet, limited new clinical information that has emerged from the many PET centres around the world, and stresses that it takes more than an expensive emission tomograph to produce worthwhile results It is to be hoped that a second edition of *Computed Emission Tomography* will come out in a few years time, and by then new insights into human physiology and pathophysiology will dominate over the more technical aspects of the subject.

RICHARD WISE

Computerized Tomography in Neuro-ophthalmology. By I. F. Moseley and M. D. Sanders. 1982. Pp. 302. London: Chapman and Hall. Price £27.50.

This book is the product of close collaboration in a large number of clinical problems by a radiologist and an ophthalmologist, each a well known expert in his field, who have long recognized the unique value of computed tomography in neuro-ophthalmology

The bulk of the text is divided into five chapters which discuss orbital disease, visual loss, optic nerve disease, eye movement disorders and developmental and metabolic disorders A short introductory section covers the physical principles of CT scanning and includes many helpful practical considerations. There follows a concise account of orbital and relevant cranial and intracranial anatomy, and the book's last chapter presents a discussion of the role of CT in relation to other diagnostic modalities. The text is written in a very clear and authoritative style, with a nice balance of clinical and radiological material. An excellent list of references is found at the end of each chapter.

The clinically orientated sections contain many fascinating and instructive case histories which are profusely illustrated, including many clinical photographs where abnormality of eye movement and facies is demonstrable. Fundoscopy, fluorescein angiography and visual field charting are frequently illustrated. The radiological material is mainly CT, but includes plain films, angiography and pneumoencephalography. This very extensive radiological material has been collected over a period of several years and, of course, some of the images were produced by older CT machines; each image clearly displays the relevant feature.

A wealth of clinical and radiological material is presented in this attractive volume which, no doubt as intended, should appeal equally to clinical and radiological specialists.

It was a pleasure to read this book, and a continuing education and entertainment to browse through the individual case histories. I strongly recommend it to all clinicians interested in neuro-ophthalmology, and I am sure that every radiologist would benefit from and enjoy reading it.

A. R. VALENTINE

Ataxia-telangiectasia. A Cellular and Molecular Link between Cancer, Neuropathology and Immune Deficiency. Edited by B. A. Bridges and D. G. Harnden. 1982. Pp. 402. Chichester: John Wiley. Price £19.75.

The DNA in our cells is under repeated attack from physical and chemical agents—radiation, increased temperature, food additives and contaminants, dyes and so on—with the capacity of altering its structure. The correct sequence of information in DNA strands is essential for normal proteins to be synthesized, and erroneous information transfer from DNA can have severely damaging effects. Wrong proteins can appear and essential metabolic and regulatory mechanisms can be disrupted. The end result of such changes could be cell death or uncontrolled cell proliferation. It is as well that evolution has equipped our cells with an array of enzymes whose function is to identify and repair any acquired aberrations in the DNA strand; enzymes, which, while still incompletely defined, appear more and more to be the same as those that are involved in DNA replication Through these enzymes the fidelity of transmission of genetic information, and the accuracy of macromolecule synthesis, are assured.

The importance of effective DNA repair in man was shown by Cleaver's discovery in 1968 that skin fibroblasts from patients with xeroderma pigmentosum (XP) were defective in their ability to make good the damage induced in DNA by ultraviolet light. In XP extreme cutaneous photosensitivity is present from an early age. Exposed skin is severely affected, with scarring and the inevitable development of epidermal malignancies of various types. A defect in the enzymic excision and repair of ultraviolet-induced cyclobutane pyrimidine dimers in DNA was demonstrated *in vivo.*

It was later found that cellular sensitivity to ultraviolet, a measure of the severity of the biochemical lesion, was greatest in those rare patients with neurological as well as cutaneous manifestations of the disease. These may include cerebral cortical atrophy and features of olivopontocerebellar atrophy and spinocerebellar disease, though in badly affected patients virtually all long-axoned neuronal populations seem involved. While nerve cell loss could be an independent manifestation of the genetic disorder, it is reasonable to ask if this too could result from defective DNA repair. Certainly large neurons, present from before birth and unable to renew, and with huge, intensely metabolically active cytoplasmic volumes, would appear to be a big target for any process which could derange protein synthesis.

The suggestion that defective DNA repair may be at the heart of obscure (pathogenetically speaking) degenerative disease of the nervous system has attracted some attention over the past six years or so. Claims of increased cellular sensitivity to radiation *in vitro* have been made for Huntington's chorea, Friedreich's ataxia and familial dysautonomia, *inter alia*, suggesting the possibility of a DNA repair defect. However, these conditions have as yet been little studied, and definitive statements have yet to be made. In contrast is a wealth of information about a disorder in which extreme radiosensitivity is present at the cellular level and in which neuronal degeneration is a constant feature. This is ataxia telangiectasia, the subject of this most important book.

Ataxia telangiectasia (AT) was recognised in neurological circles 15 years before Mme Louis-Bar's description of the clinical syndrome in 1941. By the late 1950s its delineation was virtually complete. The first indications that patients with AT showed abnormal radiation reactions to normal doses of x-rays, given for deep-seated lymphomas, were evident in 1967–1968, and these led to the investigation of cellular radiosensitivity in this disorder. A team of authors, including the editors and other contributors to this volume, found in 1975 that AT skin fibroblasts were indeed very sensitive to gamma irradiation, as measured by clonal growth. This book examines laboratory findings and summarizes the clinical aspects of the condition.

The first third of the book consists of clinical and experimental review articles, and deals with immunopathology, cytogenetics and cancer epidemiology as well as neurological and DNA repair deficiency-orientated studies. Research reports, a reminder that this book arose from a conference, make up the latter two-thirds. There is detailed examination of the possible links between defective DNA repair and cancer and immune deficiency, though little on its relationship to neuronal disease.

It is perplexing that while no-one doubts that deficient maintenance of DNA exists in AT, there is still no agreement on the nature of the defect present, a number of early suggestions having remained unconfirmed.

P. D. Lewis

Regulatory Peptides of Gut and Brain. *British Medical Bulletin*, Volume 38. Edited by R. A. Gregory 1982. Pp. 318. Edinburgh: Churchill Livingstone. Price £9.50

This issue of *British Medical Bulletin* reflects the state of the art in research on neuroactive peptides, with particular emphasis on peripheral systems. A number of basic concepts are revised in the light of the emerging new generation of peptides with transmitter-like characteristics. The volume has been edited by Dr Gregory who has been able to attract a number of distinguished researchers to summarize the main current ideas of their field of investigation. The volume covers a variety of topics such as the reanalysis of the so-called APUD theory, developmental and comparative studies, enteric nervous system, chemical aspects, electrophysiological actions, pathology, hormonal mechanisms and their coexistence with amines. The biological actions of a number of these peptides are also revised—separately in the case of substance P, vasoactive intestinal polypeptide, and neurotensin.

As is characteristic of these *British Medical Bulletins*, the chapters are full of up-to-date information concentrating on the core of the problems and their potential relevance to medicine. Medics and students will find it a very useful guide towards the understanding of this fast evolving area of research. Those searching for information on opioid peptides will find little or only short references to them as this will be the theme of a follow-up volume.

A C. Cuello

Recent Advances in Neuropathology, Number 2. Edited by W. T. Smith and J. B. Cavanagh. 1982. Pp. 301. Edinburgh: Churchill Livingstone. Price £23.00.

This multiauthored volume contains eleven chapters each of which summarizes the views and recent work of its contributor Some of the chapters are of fairly general interest in their scope, others deal with topics of a more limited nature. There is an authoritative chapter by Oehmichen on microglia; Cavanagh describes the comparative pathology of organophosphorus, acrylamide and hexacarbon neuropathies; in a detailed and extensively illustrated review of idiopathic faecal incontinence, Swash presents the evidence which suggests the condition is due to damage to the innervation of the anorectal musculature; chapters by Anderton (neuronal cytoskeletal proteins) and Esiri (on the applicability of new histological techniques to the study of the nervous system) point towards future fields of research. Some of the authors present their controversial or at least debatable views in a rather one-sided fashion and this reader gained the feeling of a hectoring, bullying tone which can best be illustrated by some quotes. 'The message to pathologists is that death can really no longer be certified as being due to fracture of the skull and cerebral contusions' (Adams *et al.* on brain damage in head injury); 'a comprehensive evaluation of the pathophysiology and pathobiochemistry of ischaemic brain lesions is possible only when these techniques are used in conjunction with a conventional histopathological approach' (Hossmann on ischaemic injury of the brain); 'it is essential to develop a systematic combined morphological and biochemical method of study... Only then will it be possible to begin to take advantage of these potentially valuable tools for the study of the cellular biology of nervous tissue' (Cavanagh on toxic neuropathies). Masters and Gajdusek in a useful review of spongiform encephalopathies make some statements too firmly, such as that vacuolation of superficial layers of cortex is 'non-specific'; and while stating that few spinal cords have been examined in spongiform encephalopathy, also tell us that the amyotrophic form of CJD is distinct from the spongiform encephalopathies and is untransmissible Here is another quotation—in the discussion of transmission of kuru—'there has been no convincing evidence that case-to-case transmission by non-invasive bodily contact has ever occurred, provided one allows that the act of cannibalism involves some form of invasive inoculation'. Williams is as provocative as ever about aqueduct stenosis being a secondary phenomenon and asks that 'a proponent of the theory that aqueduct stenosis was a cause of hydrocephalus should come up with some evidence'. Just what evidence would be acceptable to Williams is itself a problem, but I would like to see that challenge taken up.

L. W. DUCHEN

Neuropathology of Parasitic Infections. By W. J. Brown and M. Voge. 1982. Pp. 240. Oxford University Press. Price £18.50.

This is an informative and well-presented survey of the involvement of the nervous system by parasites and includes descriptions of pathology of the eye and skeletal muscle as well as the brain and cord. The pathological descriptions are rather brief and I thought that some of the space taken up by clinical histories and treatment, however interesting, could have been used to elaborate the neuropathology. The illustrations, including electron micrographs, are of excellent quality. A useful monograph

L. W. DUCHEN

Psychopharmacology of Old Age. Edited by David Wheatley. British Association for Psychopharmacology Monograph No. 3. 1982. Pp. 194. Oxford University Press. Price £15.00.

The new understanding of the dementia syndrome which has resulted from recent studies of Alzheimer's Disease and related disorders, has stemmed from careful quantitative neuropathological studies, neurochemical and neurotransmitter assays and new approaches to the quantification of the cognitive and behavioural defects so characteristic of the disease. Since dementia is so common, there are pressing social and economic reasons for an acceleration in the pace of investigation in the hope of finding new methods for the alleviation of the clinical features of the disorder. This short book offers reviews of a number of different approaches to the problem. On the whole, the approach is behavioural and subjective rather than neurological, but attention is also paid to pharmacological aspects. The book is divided into three parts concerning basic concepts, the cognitive disorder, and psychiatric aspects. The book begins with an interesting chapter, largely theoretical, on the nature of ageing, considered in relation to cell biology. This approach is basically unhelpful in understanding the clinical features of the clinical disorder itself but has much to commend it as a unifying thread for research. The animal model beloved of so many researchers, scrapie, receives a chapter to itself and this is a short review of the relationship between central neurotransmitter deficits, particularly that of the acetyl cholinergic system, and memory disorder in the disease. The differing pharmacokinetics of the aged and the problem of drug compliance are properly emphasized. There follow useful reviews of methods for the measurement of change in cognitive function relative to the assessment of elderly patients, but these are somewhat obscured by reports of the effects of two groups of compounds produced in the laboratories of two pharmaceutical companies. This work might have been better placed in peer-reviewed journals. The volume concludes with short reviews of anxiety, the treatment of depression and of sleep disturbances, and the assessment of paranoid psychosis in the elderly. The latter is a particularly succinct and well-constructed account of these difficult problems. This book does not attempt to provide an encyclopaedic account of the pharmacology and treatment of the different syndromes afflicting the elderly. Indeed, there is much which has been omitted. Nonetheless, there are a number of useful chapters, perhaps of more value to the psychiatrist than the neurologist. It is, perhaps, particularly relevant to notice the difficulties apparent in the interpretation of cognitive tests commonly applied to patients in the assessment of dementia when comparison is attempted from test to test. This problem of assessment is the most pressing of those currently confronting investigators working on dementia and its treatment.

MICHAEL SWASH

Phantom and Stump Pain. Edited by J. Siegfried and M. Zimmermann. 1981. Pp. 185. Berlin. Springer-Verlag. Price DM 68.00.

This volume is a collection of papers given at a symposium on stump and phantom limb pain. Neurophysiological, anatomical, and clinical aspects are considered, followed by a larger section dealing with treatment. The opening chapter by Wall provides a lucid account of the abnormal neurophysiological properties developing after nerve injury which may be substrates for pain, with details of some recent experimental findings demonstrating the wide range of the resultant abnormal physiological and pharmacological properties. Blumberg and Janig summarize the results of their experiments, showing an interaction between sympathetic efferent and sensory fibres in neuromas—evidence which provides a rationale for the therapeutic effect of sympathectomy in some nerve injury pains. These two chapters, particularly the one by Wall, summarize most of what is currently known about the physiological basis for stump and phantom pains. Wall stresses the need for careful investigation of peripheral mechanisms before attributing these pains to poorly defined central events.

Several ensuing chapters are concerned with clinical aspects, including analysis of personality factors and even the rare occurrence of phantom tooth sensations. The detailed descriptions of symptoms are interesting and draw attention to the very variable symptoms which may result from amputation. They add to the already voluminous literature concerned with the clinical phenomenology of amputation pain, but do not really contain anything new on the subject.

The section on treatment occupies the largest part of the book. A short paper on drug treatment discusses individual drugs and combinations which may help; that no fewer than ten major groups of drugs are mentioned in one page of text as being useful testifies to the fact that drugs are usually of very limited benefit, though a less critical view appears to be taken by the author. Transcutaneous electrical stimulation is discussed in four separate chapters, without any clear indication of optimal means of application emerging, though preliminary results of a method of programmed stimulation presented by Mundinger and Neumiller for transcutaneous and for mesencephalic stimulation suggest that correct impulse patterning may be of crucial importance. Their claim that the unpleasant side-effects of midbrain stimulation can be diminished by correct impulse patterning is an important one which requires further study.

Surgical measures are discussed by several contributors. Samii advocates centrocentral anastomosis in neuromas using nerve grafts to reduce neuroma pain, the rationale being that neuroma reformation is reduced. Unfortunately, tantalizingly few results are presented and we are left to look forward to further papers on this technique. A study by Narakas on brachial plexus reconstruction in root avulsion and plexus injuries would suggest that early operation leads to a lower incidence of long-term pain, but a control group of only 19 patients is compared with an operated group of 160, and the necessary statistical analysis is not presented.

Siegfried and Cetinalp review the reported effects of transcutaneous and dorsal column stimulation, dorsal root entry zone lesions, anterolateral cordotomy, mesencephalotomy, thalamotomy and deep brain stimulation, and conclude that on the whole stimulation methods now seem preferable to destructive lesions. Their paper is a short review of the growing and increasingly confusing literature on these procedures, though the conclusion is one now shared by many neurosurgeons. A subsequent paper by Krainick and Thoden is concerned exclusively with dorsal column stimulation, although some analgesia is usually obtained, the effect is often short-lived. Samii describes his experience with Nashold's substantia gelatinosa thermocoagulation technique for deafferentation pain and confirms Nashold's good results. We wait to see how long the analgesia lasts.

The multiplicity of the treatments described in this book highlights the fact that we still have no really effective, lasting means of helping most patients with stump and phantom pains. The book is a useful introduction to these topics, being relatively short and inexpensive, but it would have benefited from a more extensive consideration of scientific aspects, particularly neuropharmacological, with rationalization of some of the rather repetitive clinical accounts.

J. W. SCADDING

Handbook of Physiology. Section 1. **The Nervous System.** Volume II. **Motor Control,** Parts 1 and 2. Section Editors: J. M. Brookhart and V. B. Mountcastle. Volume Editor: V. B. Brooks. 1981. Pp. 1–733 and 735–1480. Bethesda, Maryland: American Physiological Society. Price $145.00 (two volumes).

These two volumes provide an interdisciplinary account of the control of movement. Their scope is wide, the topics covered ranging from mechanics and the physiology of muscle and nerve on the one hand to the behavioural aspects of motor performance on the other. The middle ground, and indeed the largest proportion of the books, is taken up by accounts of the anatomical and physiological principles underlying the control of movement by the central nervous system. Both parts are divided into subsections which deal with major fields and contain two or more chapters on more specific topics. Part 1 is divided into Bones, Muscles and Transmitters (Chapters 2–5), Reflexes, Neural Organization, and Control Systems (Chapters 6–12) and Descending Control Pathways (Chapters 13–15). Part 2 contains Cerebellum and Basal Ganglia (Chapters 16–21), Cerebral Control Mechanisms (Chapters 22–25), Rhythmical Movements and Their Voluntary Engagement (Chapters 26 and 27), Visuomotor Control (Chapters 28 and 29) and Behavioural Motor Performance (Chapters 30–33). Each chapter is written by different contributors who are experts in their particular field. Their names include some of the giants of contemporary experimental neuroanatomy and neurophysiology.

As one would expect, therefore, most of the material is presented in an up-to-date and authoritative fashion. Some chapters contain significant historical review components which are particularly useful. One of the excellent features of these volumes is that the authors have frequently cited original articles and thus most chapters contain extensive bibliographies which will be most helpful to those wishing for more detailed information. A large proportion of the illustrations come from original articles or other published work and their standard is generally high.

Although there are frequent cross references between chapters which enhance the feeling of a coordinated approach there are also occasional lapses. Examples include contradictions in nomenclature used by anatomists or physiologists for certain brain nuclei and in at least one instance the use of different names by different authors for the same structure. This may be a source of either amusement or annoyance to the *cognoscenti* but would certainly confuse the reader consulting the field for the first time.

This relatively minor complaint apart, these volumes are not only a pleasure to read but contain a wealth of information and ideas. They can be warmly recommended to anyone wishing for a comprehensive account of the state of knowledge and the direction of current research in the field of motor control.

A. R. CROSSMAN

Music, Mind, and Brain. The Neuropsychology of Music. Edited by Manfred Clynes. 1982. Pp. 430. New York and London: Plenum Press. Price $39.50.

This book consists largely of communications made at a conference on the Physical and Neuropsychological Foundations of Music at Ossiach in 1980. Contributors include workers in psychology, musicology, computers, communication and acoustics. The sectional topics are titled Concerning the Language of Music, Music and Neurobiologic Function, and Concerning Music and Computers. The diligent reader will find some interesting observations on 'The Pitch Set as a Level of Description for Studying Musical Pitch Perception' by Balzano, while Terhardt and Hartmann write informatively on computers and electronic music. Toop of Sydney concludes the book with an informed chapter on New Music and Neurobiologic Research, for psychologists and others working in the field tend, like British concert audiences, to direct their attention to 18th- and 19th-century compositions.

Music, Mind and Brain is definitely for the specialist, to whom it is commended.

R. A. HENSON

FORTHCOMING EVENT

Thirteenth International Summer School of Brain Research

Every two years The Netherlands Institute for Brain Research and the University of Amsterdam organize an International Summer School of Brain Research. The Thirteenth Summer School, to be held in Amsterdam from August 22 to 26, 1983, is organized by G. J. de Vries, J. P. C. de Bruin, M. A. Corner, D. F. Swaab, H. H. Swanson and H. B. M. Uylings, and will take place at the Royal Netherlands Academy of Sciences (Kloveniersburgwal 29). The school will be devoted to the theme 'Sex Differences in the Brain—Relation between Structure and Function'.

Lectures will be given by W. W. Beatty (USA), C. P. Benbow (USA), S. M. Breedlove (USA), S. Butler (England), G. J. de Vries (The Netherlands), K. D. Döhler (FDR), R. G. Dyer (England), R. A. Gorski (USA), M. E. Gurney (USA), J. B. Hutchison (England), E. B. Keverne (England), D. Kimura (Canada), H. F. L. Meyer-Bahlburg (USA), B. J Meyerson (Sweden), R. L. Moss (USA), D. W. Pfaff (USA), J. M. Reinisch (USA), P. Södersten (Sweden), D. F. Swaab (The Netherlands), C. D. Toran-Allerand (USA) and N. E. van de Poll (The Netherlands).

For more detailed information, please contact Miss J. Sels, The Netherlands Institute for Brain Research, 28 Ijdijk, 1095 KJ Amsterdam, The Netherlands (tel. 020-948532).

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Brain

A JOURNAL OF NEUROLOGY

VOLUME 106 · PART III · SEPTEMBER 1983

Painful epileptic seizures. G. Bryan Young and Warren T. Blume 537

Ocular motor deficits in Parkinson's disease: I. The horizontal vestibulo-ocular reflex and its regulation. Owen B. White, Jean A. Saint-Cyr and James A. Sharpe 555

Ocular motor deficits in Parkinson's disease: II. Control of the saccadic and smooth pursuit systems. Owen B. White, Jean A. Saint-Cyr, R. David Tomlinson and James A. Sharpe 571

Microneurographic evidence of excessive sympathetic outflow in the Guillain-Barré syndrome. Jan Fagius and B. Gunnar Wallin 589

Motor activity and muscle properties in the hemidecerebellate cat. Jan-Willem Stenvers, Otto Eerbeek, J. M. B. Vianney de Jong and A. E. F. Hugo Meijer 601

Drawing objects from memory in aphasia. Guido Gainotti, Maria Caterina Silveri, Giampiero Villa and Carlo Caltagirone 613

Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential): the unconscious initiation of a freely voluntary act. Benjamin Libet, Curtis A. Gleason, Elwood W. Wright and Dennis K. Pearl 623

Spontaneous eye-blink rates and dopaminergic systems. Craig N. Karson 643

Deficits in attention and movement following the removal of postarcuate (area 6) and prearcuate (area 8) cortex in Macaque monkeys. G. Rizzolatti, M. Matelli and G. Pavesi 655

The long-term effects of removal of sensorimotor cortex in infant and adult Rhesus monkeys. R. E. Passingham, V. H. Perry and F. Wilkinson 675

An anatomical study of the effects of unilateral removal of sensorimotor cortex in infant monkeys on the subcortical projections of the contralateral sensorimotor cortex. J. J. Sloper, P. Brodal and T. P. S. Powell 707

Benign X-linked myopathy with acanthocytes (McLeod syndrome): its relationship to X-linked muscular dystrophy. M. Swash, M. S. Schwartz, N. D. Carter, R. Heath, M. Leak and K. Ll. Rogers 717

From 4 to four: a supplement to 'from three to 3'. Xavier Seron and Gérard Deloche 735

Peripheral projections of fascicles in the human median nerve. W. Schady, J. L. Ochoa, H. E. Torebjörk and L. S. Chen 745

Cerebral glucose utilization, as measured with positron emission tomography in 21 resting healthy men between the ages of 21 and 83 years. R. Duara, R. A. Margolin, E. A. Robertson-Tchabo, E. D. London, M. Schwartz, J. W. Renfrew, B. J. Koziarz, M. Sundarum, C. Grady, A. M. Moore, D. H. Ingvar, L. Sokoloff, H. Weingartner, R. M. Kessler, R. G. Manning, M. A. Channing, N. R. Cutler and S. I. Rapoport 761

Notices of recent publications 777

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Brain

A JOURNAL OF NEUROLOGY

VOLUME 106 · PART III · SEPTEMBER 1983

Painful epileptic seizures. G. Bryan Young and Warren T. Blume 537

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Ocular motor deficits in Parkinson's disease: II. Control of the saccadic and smooth pursuit systems. Owen B. White, Jean A. Saint-Cyr, R. David Tomlinson and James A. Sharpe 571

Microneurographic evidence of excessive sympathetic outflow in the Guillain-Barré syndrome. Jan Fagius and B. Gunnar Wallin 589

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Drawing objects from memory in aphasia. Guido Gainotti, Maria Caterina Silveri, Giampiero Villa and Carlo Caltagirone 613

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Benign X-linked myopathy with acanthocytes (McLeod syndrome): its relationship to X-linked muscular dystrophy. M. Swash, M. S. Schwartz, N. D. Carter, R. Heath, M. Leak and K. Ll. Rogers 717

From 4 to four: a supplement to 'from three to 3'. Xavier Seron and Gérard Deloche 735

Peripheral projections of fascicles in the human median nerve. W. Schady, J. L. Ochoa, H. E. Torebjörk and L. S. Chen 745

Cerebral glucose utilization, as measured with positron emission tomography in 21 resting healthy men between the ages of 21 and 83 years. R. Duara, R. A. Margolin, E. A. Robertson-Tchabo, E. D. London, M. Schwartz, J. W. Renfrew, B. J. Koziarz, M. Sundarum, C. Grady, A. M. Moore, D. H. Ingvar, L. Sokoloff, H. Weingartner, R. M. Kessler, R. G. Manning, M. A. Channing, N. R. Cutler and S. I. Rapoport 761

Notices of recent publications 777

British Journal of Psychology

Contents of volume 73, Part 4, November 1982

S. T. Kempley & J. Morton. The effects of priming with regularly and irregularly related words in auditory word recognition

R. S. Johnston. Phonological coding in dyslexic readers

M. E. Thomson. The assessment of children with specific reading difficulties (dyslexia) using the British Ability Scales

J. Wilding, N. Mohindra & K. Breen-Lewis. Noise effects in free recall with different orienting tasks

E. E. Schultz, Jr & R. Johnson. Proactive effects in memory for stories

M. G. Riseborough. Meaning in movement: An investigation into the interrelationship of physiographic gestures and speech in seven-year-olds

S. Sveback, O. Storfjell & K. Dalen. The effect of threatening context upon motivation and task-induced physiological changes

W. H. James. The IQ advantage of the heavier twin

A. Slater, V. Morison & D. Rose. Visual memory at birth

M. M. Smyth & J. E. Kennedy. Orientation and spatial representation within multiple frames of reference

E. Govier & M. Pitts. The contextual disambiguation of a polysemous word in an unattended message

Book reviews

British Journal of Psychology, edited by Max Coltheart, Birkbeck College, London, is published quartely. Part 2 (1982) was a Special Issue on Piaget: Issues and Experiments and is available as a separate casebound issue price £5.95(US$11.95)

Volume 73 (1982) £47.00(US$100.00), Volume 74 (1983) £51.00(US$110.00)

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British Journal of Psychology

Contents of volume 74, Part 2, May 1983

E. Funnell. Phonological processes in reading: New evidence from acquired dyslexia

G. Stanley, G. A. Smith & E. A. Howell. Eye-movements and sequential tracking in dyslexic and control children

G. Th. Pavlidis. Erratic sequential eye-movements in dyslexics: Comments and reply to Stanley *et al*

G. Stanley, G. A. Smith & E. A. Howell. Eye-movements in dyslexic children: Comments on Pavlidis' reply

M. Hojat. Comparison of transitory and chronic loners on selected personality variables

J. Hartley & D. Rooum. Sir Cyril Burt and typography: A re-evaluation

B. D. Smith & F. Principato. Effects of conflict and field structure on arousal and motor responses

S. E. Gathercole, V. H. Gregg & J. M. Gardiner. Influences of delayed distraction on the modality effect in free recall

J. P. Harris. Age, sex and time of day effects on the duration of the movement after-effect

G. Cohen & D. Faulkner. Word recognition: Age differences in contextual facilitation effects

D. Kilshaw & M. Annett. Right- and left-hand skill I. Effects of age, sex and hand preference showing superior skill in left-handers

M. Annett & D. Kilshaw. Right- and left-hand skill II: Estimating the parameters of the distribution of L—R differences in males and females

Book reviews

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The Genetics of Neurological Disorders

Michael Baraitser

This completely new book is a successor to Pratt's very successful work of the same title, now out of print. As with the other volumes in the series, it is clinically orientated and aims at comprehensiveness in both text and references. It is illustrated with 39 clinical plates. These make it invaluable to practising neurologists, to whom the assessments of the risk of recurrence of neurological disorders will also prove most useful. Illustrated £35 *Oxford Monographs on Medical Genetics*

Neurobehavioural Consequences of Closed Head Injury

Harvey S. Levin, Arthur L. Benton and Robert G. Grossman

The personal, social and economic consequences of head injuries can scarcely be over-estimated. This book covers the full range of effects on behaviour, both initial and long term. It is based primarily on a review of research rather than impressions from clinical experience; however, it integrates clinical knowledge with findings from experimental studies. Head injury sequelae in both children and adults are discussed. The methods for measuring coma and acute amnesia after head injury are presented. Illustrated £20

Synopsis of Neuroanatomy

Howard A. Matzke and Floyd M. Flotz

Widely used as an introduction to and review of neuroanatomy, by undergraduate and medical students, this book has been updated throughout for the fourth edition. New material has been added on topics such as neurotransmitters, laminae of spinal cord gray matter, nociceptors, muscle spindles, the spinothalmic tract, cellular organization of the visual system, locus ceruleus and raphe nuclei, and the blood-brain barrier. Fourth edition illustrated £7.50

Precursors of Stroke

Etiologic, Preventive and Therapeutic Implications

Bruce S. Schoenberg

This research monograph provides the most detailed and well documented epidemiologic description to date of the relation between cardiovascular and cerebrovascular disease. It demonstrates that valvular heart disease, diabetes mellitus and transient ischemic attacks (TIA) increase the risk of ischemic stroke. These findings derive from the retrospective and prospective analysis of very high quality data. The analysis shows what the time interval is between the onset of cardiovascular diseases and of stroke, and how much influence the various forms of hypertension and heart disease have on survival once stroke has occurred. £9.95

Oxford University Press

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Autonomic Failure

A Textbook of Clinical Disorders of the Autonomic Nervous System

Edited by Sir Roger Bannister

This book aims to provide clinicians with a guide to useful tests which are needed to identify autonomic defects of particular organs in which they have an interest. The interpretation of these tests is set against the more general background of physiology and pathology of the autonomic nervous system, in order to form a basis for rational management of the patient in a field which is generally recognized to be exceedingly difficult. Illustrated £45

Contributions to Neuropsychological Assessment

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PAINFUL EPILEPTIC SEIZURES

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SUMMARY

Out of 858 epileptic patients, 24 had painful seizures. Three distinct groups emerged: (1) those with unilateral pain in the face, arm, leg or trunk (Unilateral Group)—10 cases; (2) a Cephalic Group with pain restricted to the head—11 cases; and (3) an Abdominal Group with central abdominal pain—3 cases.

Unilateral pain consistently implicated ictal involvement of the contralateral rolandic region at the time of pain. In most cases it was probably due to involvement of the primary somatosensory cortex (SI). Cephalic pain did not localize the site of seizure origin. In most cases it probably arose by a vascular mechanism. Abdominal ictal pain reflected temporal lobe epileptic activity in our cases. The mechanism of its production is uncertain, but it is unlikely to be due to a peripheral (for example gastrointestinal) mechanism.

INTRODUCTION

Occasionally patients experience pain during epileptic seizures. Gowers (1901) first described pain occurring with seizures and described 3 varieties: hemicorporeal (unilateral), cephalic and abdominal (visceral or pneumogastric). In this paper we review our patients with these three types of painful seizures to assess their relative incidences, to determine the localizing value each has for seizure origin and spread and to review possible pathophysiological mechanisms of each.

METHODS AND MATERIAL

We defined painful epileptic seizures as attacks in which the patient used the term 'pain' to describe a symptom which occurred first or among a series of ictal events. We took care to ascertain that the sensation actually did 'hurt'. We accepted only those patients who were capable of giving a consistent and reliable history; this included those with mental subnormality. Patients with only postictal pain such as headache, or preictal pain which did not appear to be part of the seizure, were excluded. Out of 858 epileptic patients followed in our clinics, 24 (2.8 per cent) met these criteria.

The 24 cases were easily categorized into 3 groups: (1) unilateral pain in face, arm, leg or trunk (unilateral group); (2) pain restricted to the scalp or calvarial region (cephalic group); and (3) central abdominal pain (abdominal group). The site of seizure origin was determined by other clinical features of each seizure and by findings on electroencephalography (EEG). The latter included interictal epileptiform discharges and/or recorded electrographic seizures with or without clinical accompaniment.

TABLE 1 UNILATERAL GROUP

Case	*Age (yrs)*	*Sex*	*Site of pain*	*Sequence of ictal events*	*EEG data*	*Definite or probable site of seizure origin*	*Quality of pain*	*Cerebral lesion and aetiology*	*Neurological deficits*
1	14	F	L forearm → L shoulder	Pain L forearm → shoulder → macropsia → grand mal	R central sharp waves Recorded seizure R central	R postcentral gyrus	'Burning-tingling' → 'shooting'	Gliotic area R lower rolandic area Peri- or antenatal insult	Congenital L hemiparesis Analgesic and anaesthetic L hand. Hyperaesthesia L face, arm, leg, upper trunk
2	19	F	L calf	'Odd feeling' L toes → twitching L foot → L calf → pain L calf → tonic head extension → head and eyes to L	Central sagittal R central spikes, independent R occipital spikes	R rolandic region	'Cramping'	Chronic 'focal encephalitis'	None interictally
3	25	F	R arm	Paraesthesiae R shoulder → R arm → tonic stiffening R arm and leg	Multiple independent spikes, maximal R frontal	L postcentral gyrus		Measles encephalitis, aged 4 yrs	
4	25	M	R arm	Paraesthesiae R palm → fingers → shoulder → face → thorax → leg (all R) → tonic R side → clonic jerks R side with pain R arm	L occipitoparietal and L frontal spikes and sharp waves Absent alpha activity on L	L parietal	'Like a thousand bee stings'	Porencephaly L parietal-occipital, shrunken gyri behind postcentral sulcus (at operation) Perinatal insult	R homonymous hemianopia Poor fine movements R hand Impaired proprioception and stereognosis R hand
5	16	M	L shoulder, L arm and L face	Paraesthesiae L shoulder → L arm → L face → pain same distribution → tonic L arm → deviation of head and eyes to L	Central sagittal sharp waves. Recorded seizures central sagittal-R central	R postcentral gyrus	'Like white noise'	Unknown	Impaired L foot movements

6	11	M	R arm	Vocalization → pain R arm → generalized clonic seizure	L central-parietal-temporal spikes Recorded seizure L central-parietal-temporal	L rolandic-parietal-temporal	—	Trauma	Mental subnormality Mild R hemiparesis
7	28	F	L retro-auricular, L shoulder	Illusion of body movement, tight L cheek → L retro-auricular pain → L shoulder pain → loss of feeling L arm and leg → L sided tonic → L sided clonic → generalized clonic	Recorded seizure R parietal-occipital-posterior temporal → R anterior-mid-temporal → diffuse R hemisphere then generalized	R parietal-occipital posterior temporal	'Achey'	Unknown	—
8	16	F	L arm	L arm pain → clonic jerks L hand → arm → generalized clonic seizure	Normal	R hemisphere	'Like an electric shock'	Unknown	Odd posturing L arm
9	35	F	R hip	Throbbing feeling R hip → trunk → more intense → pain R hip and trunk → clonic jerks R hip	L parietal theta activity	L parietal	'Throbbing'	Metastatic malignant melanoma L anterior superior parietal lobe	—
10	11	M	R ala of nose → R eye	Pain → speech arrest → head and eyes to L → generalized tonic seizure	Recorded seizures L hemisphere → generalized	L hemisphere	'Like a vibrating knife'	Unknown	—

CASE REPORTS

Unilateral Group

This group contains 6 female and 4 male patients from 11 to 35 years of age. The features of each case are summarized in Table I.

Case 1. A 14-year-old girl with a congenital left hemiparesis developed seizures when aged 10 years. The seizures began with a 'burning, tingling pain' in the left forearm which progressed to a 'shooting pain' to the left shoulder. This sometimes proceeded to macropsia and then a generalized tonic-clonic seizure. On examination her paresis was most marked in her left arm and hand. The small left hand was analgesic and anaesthetic distal to the wrist, with pin prick sensation reduced but still perceived in the remainder of the left upper limb, left upper thorax, left side of the neck and left lower face. Position sense was impaired in the left wrist. A seizure recorded on the EEG showed reduction in voltage in the right central region just prior to the onset of left arm pain (fig. 1). Quasiperiodic right central sharp waves followed this flattening.

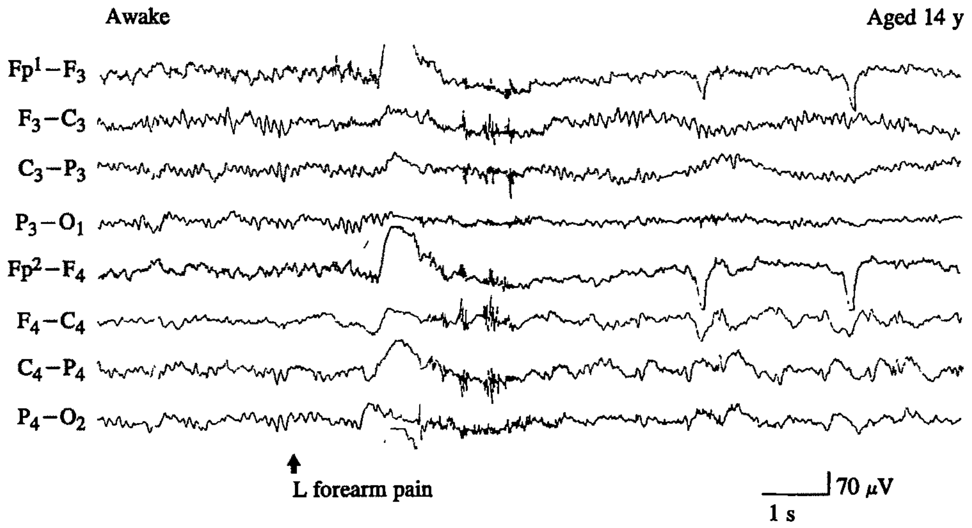

FIG. 1. EEG recording during painful seizure in *Case 1*. A reduction of right central rhythms is seen in the preictal portion of the tracings. Coincident with the onset of left forearm pain is attenuation of right fronto-central activity, followed by periodic right central (C_4) spikes and right central-parietal (C_4-P_4) delta waves. Artefact at C_3 during seizure.

At operation, an area of shrunken gliotic cortex was present in the postcentral gyrus and superior temporal area on the right. This shrunken area probably included the 'hand area' as stimulation just above this area produced a sensation of tingling in the left forearm (fig. 2). Cortical epileptiform activity was present superior and posterior to the gliotic area on the postcentral gyrus. Resection of the atrophic area and immediately adjacent cortex relieved her of her seizures. Her sensory deficit was only slightly increased. Histologically, neuroglial nodules were present in the meninges. The cortex showed a disorganized neuronal arrangement with dense gliosis and foci of calcification.

Case 2. This 19-year-old girl began to have nocturnal generalized convulsions followed by postictal left hemiparesis when aged 10 years. By 17 years her attacks began with 'an odd feeling' in the toes of the left foot followed by twitching of the same foot and then of the calf. Cramp-like pain was felt in the left calf coincident with the twitching. The seizure often progressed to tonic extension of the head and leftward deviation of the eyes. More recently, occasional seizures began with leftward ocular and

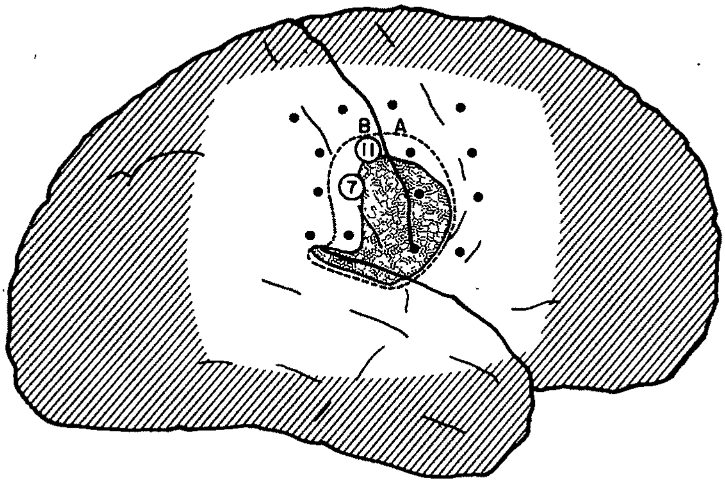

FIG. 2. *Case 1.* The nonlined area was exposed at operation. The dashed line delimits the excision. The stippled area is atrophic gliotic cortex. Stimulation at A produced flexion of the forearm and hand, and at B, left forearm tingling. The dots represent electrocorticogram electrode placements. The principal spikes were recorded at 7 and 11.

cephalic deviation with speech arrest and/or flashing lights in the left visual field. Neurological examination was normal. The EEG showed frequent central sagittal-right central spikes, with sporadic spikes occurring independently in the right occipital region. Computerized tomography (CT) showed widened sulci on the right superior parietal and right perisylvian regions.

At operation electrocorticography revealed multifocal spiking without predominence of any single region. Biopsy of the right superior and middle frontal gyri and a limited precentral resection showed a chronic focal encephalitis similar to that described by Rasmussen *et al.*, (1958).

Case 3. This 25-year-old woman had a history of measles encephalitis at 4 years of age. She recovered from this and was well until seizures began when aged 21 years. Initial paraesthesiae in the right shoulder spread to the arm, followed by pain in the right arm and then tonic stiffening of the right arm and leg. The EEG showed multiple independent spikes, most frequent in the right frontal region.

Case 4. This 25-year-old man who had a mild congenital right hemiparesis developed seizures when aged 10 years. Initial paraesthesiae in the right palm spread to the fingers, then sequentially to the shoulder, the face, the thorax and leg (all on the right side). This was followed by tonic right-sided posturing and then clonic jerks on the right side of the body associated with pain in the right arm 'like a thousand bee stings'. Examination showed a dense right homonymous hemianopia, poor fine movements of the right hand and impaired proprioception and stereognosis in the right hand. The EEG showed frequent left occipitoparietal and left frontal spikes and sharp waves. Alpha activity was absent on the left. A CT scan showed a porencephalic cyst involving the left parieto-occipital region. At operation the postcentral gyrus was shrunken. With electrocorticography spikes were mainly present above the superior part of the cyst. Subpial resection of the margins of the cyst was followed by relief from seizures. On histological examination, extensive gliosis and intracortical calcification were present, as well as heterotopic areas of grey matter.

Case 5. This 16-year-old boy developed seizures when aged 10 years. These began with paraesthesiae in the left shoulder spreading to the left arm then marching to the face, after which pain 'like white noise' spread in the same manner. This was followed by tonic posturing of the left arm and deviation of the head and eyes to the left. Mild impairment of left foot movements constituted the only abnormality on examination. The EEG showed occasional central sagittal sharp waves. Recorded seizures began with a 30 to 35 Hz rhythm in the central sagittal-right central regions. A CT scan showed an atrophic area in the right central area near the vertex.

Case 6. This 11-year-old boy suffered a severe head injury at the age of 1 year that left him with moderate mental subnormality and a right hemiparesis. The seizures began one year after the accident. His most frequent seizure consisted of a yell, then pain in the right arm followed by bilateral clonic movements. Other seizures began with turning the head to the right with the right arm abducted at the shoulder. The EEG showed frequent left central-parietal-temporal spikes. Voltage was reduced from the left hemisphere. Sleep activated electrographic seizures in the left central-parietal-posterior temporal regions as rhythmic 14 to 16 Hz waves. At operation, electrocorticography showed epileptiform activity maximal in the region of the supramarginal gyrus at the posterior end of the left sylvian fissure with recorded seizures from the anterior temporal lobe, posterior frontal and central regions. Resection of the anterior left temporal lobe and left frontal lobe reduced the seizure frequency, although frequent epileptiform potentials were present in the rolandic region.

Case 7. This 28-year-old woman had a five year history of seizures. During these she lost awareness with generalized convulsions. These proved difficult to control medically. A seizure occurred while an EEG was recorded. She was attended prior to and during this seizure by a physician who carefully noted each symptom and examined the patient during the seizure. It began with an illusion of body movement followed by tightness in the left cheek. She then noted an 'achey' left retroauricular pain which spread to the left shoulder. This was followed by subjective left-sided numbness with loss of pin prick sensation in the left arm and leg. Left-sided tonic posturing then occurred followed by left-sided clonic movements leading to a generalized clonic seizure. The recorded seizure began with rhythmic waves in the right parietal-occipital-posterior temporal area which spread to the right anterior-midtemporal region and then diffusely in the right hemisphere, finally becoming generalized. Other investigations were negative.

Case 8. This 16-year-old girl had an hour long generalized convulsion when aged 14 months. She subsequently had recurring generalized convulsions, some of which began with a left arm pain which felt 'like an electric shock'. This sensation was followed by clonic jerking of the left hand, spreading up the arm to the shoulder and then a generalized clonic seizure occurred. On examination she showed borderline intelligence and odd posturing of the left arm. Investigations, including EEG, were negative.

Case 9. This 35-year-old woman with metastatic malignant melanoma developed seizures beginning with a throbbing sensation in the right hip, moving up to the trunk, unaccompanied by movement. This sensation became more intense until she noticed pain in the right hip and trunk. She then developed clonic movements of the right hip. Neurological examination was negative. An EEG showed 4 to 7 Hz low voltage waves in the left parietal region as the only abnormality. A CT scan revealed a metastatic lesion in the left superior parietal lobe with minimal oedema.

Case 10. This 11-year-old boy developed seizures when aged 7 years. These seizures all began with pain 'like a sharp knife' in the right ala of the nose. As this spread up the right side of the nose to the right eye the pain was felt like a 'vibrating knife'. Then there was speech arrest followed by turning of the head and eyes to the left with unresponsiveness. A generalized tonic seizure sometimes ensued. Examination was negative. The EEG showed sporadic left temporal lobe spikes. A recorded clinical and electrographic seizure began with 30 Hz low voltage waves in the left hemisphere. The rate slowed to 10 Hz saw-toothed waves. Then generalized 5/s spike and wave activity occurred. Other investigations were negative.

Cephalic Group

Six female and 5 male patients ranging in age from 10 to 46 years comprised this group (Table 2).

Case 11. This 21-year-old girl began having seizures when aged 12 years. Four types of seizures occurred, the most frequent beginning with a throbbing, left parietal headache immediately followed by hearing a 'beeping noise'. Her arms trembled and she saw flashing coloured lights in the left visual field. After this she lost consciousness and had a generalized tonic-clonic seizure. Neurological and general physical examination was negative. The EEG showed independent bioccipital and posterior temporal spikes, maximal on the right. Electrographic seizures, unaccompanied by clinical symptoms, began with rhythmic saw-toothed 5 Hz waves in the right posterior temporal-occipital region. The cause of the seizures is unknown.

Case 12. This 13-year-old girl had an infantile left hemiparesis. She developed seizures that began with vertigo followed by diffuse headache and then visual disturbance and a generalized clonic seizure. In addition to the mild left hemiparesis, she showed diminished two-point discrimination in the left hand. The EEG revealed right occipital spikes spreading to the right central region after a 175 ms delay.

Case 13. This 18-year-old boy had seizures since the age of 12 years. These began with pain in the right temporal region lasting a few seconds followed by loss of consciousness with either right- or left-sided tonic posturing. Examination showed mental subnormality and a higher sensory threshold on the left side of the body as the only neurological abnormalities. The cause of the seizures was unknown. The EEG showed sharp and slow wave complexes at 2 to 2.5 Hz in the right temporal region. With seizures, these sharp and slow wave complexes were more persistent, spread into the right frontal area, and then became generalized as secondary bilateral synchrony. Postictally, low voltage waves of less than 3 Hz were present in the right hemisphere.

Case 14. This 13-year-old right-handed boy's seizures began at the age of 6 years. An initial feeling 'that everything was familiar' was followed by a generalized headache, then loss of awareness for 3 to 4 min. On examination he showed impaired fine finger movements on the left. The seizures were thought to be due to head trauma in the past. The EEG showed 4 to 5 Hz waves in the left temporal region as the only abnormality.

Case 15. This 46-year-old man had a one year history of seizures. 'Sharp, severe' headache in the right supraorbital area was followed by loss of consciousness with deviation of head and eyes to the left and then a generalized tonic-clonic seizure. Examination postictally was normal. The EEG showed medium voltage 2 to 3 Hz arrhythmic waves in the right occipital-posterior temporal region. An electrographic seizure without clinical accompaniment was recorded. It consisted of 15 Hz medium voltage rhythmic waves in the right occipital region with some spread to the posterior temporal and right parietal area lasting 30 s followed by a 4 to 5 Hz medium voltage wave in the same region. A CT scan showed increased density in the right posterior temporal-occipital region. The histological nature of the lesion is not yet known.

Case 16. This 20-year-old girl had generalized tonic-clonic seizures from her early childhood until aged 16 years when she had seizures beginning with a sharp pain in the left temple then in both temporal regions. After this she had a sensation of 'needles pricking the scalp' especially at the vertex, and then would lose awareness, stare blankly and have automatisms. Examination was negative. The EEG showed occasional sharp waves in the right temporal region.

Case 17. This 12-year-old boy had a two year history of attacks beginning with a throbbing, right occipital headache followed by difficulty with comprehension of speech, then 'wavy lines' in his visual fields. On one occasion this has proceeded to a generalized tonic-clonic seizure. His past history was otherwise negative. The family history was strongly positive for classical migraine. Examination was normal. The EEG showed fairly frequent right occipito-parietal spikes. The dichotic listening test indicated speech representation in the right cerebral hemisphere. A CT scan was normal.

Case 18. This 10-year-old boy had seizures from 2½ years of age following a head injury. His most common type of seizure began with left-sided head pain near the eyes, followed by tonic contraction and twitching of the left side of the face. The left arm then developed tonic extension. The past history was negative. He was of normal intelligence and neurological examination was normal. The EEG has shown a slow wave abnormality in the right cerebral hemisphere with multiple independent right hemisphere spikes, maximal in the frontotemporal area.

Case 19. This 11-year-old girl, who was born prematurely, had a mild congenital right hemiparesis. Seizures began at the age of 6 years with a steady generalized headache followed by true vertigo, then flashing lights in the visual fields progressing to a generalized tonic-clonic seizure. The EEG showed spikes in the right midtemporal region and a nonspecific abnormality occipitally, maximal on the left.

TABLE 2. CEPHALIC GROUP

Case	*Age (yrs)*	*Sex*	*Site of pain*	*Sequence of ictal events*	*EEG data*	*Definite or probable site of seizure origin*	*Quality of pain*	*Cerebral lesion and aetiology*	*Neurological deficits*
11	21	F	L parietal	L-sided headache → 'Beeping noise' → arms trembled → flashing lights L visual field → grand mal	Independent bioccipital posterior temporal spikes, maximal R Electrographic seizures, origin R posterior temporal	R temporal	Throbbing	Unknown	None
12	13	F	Generalized over scalp	Vertigo → diffuse headache → visual disturbance → generalized clonic	R occipital spikes spread to R central after 175 ms	R parietooccipital	—	Unknown	Mild L hemiparesis and reduced 2-point discrimination left hand
13	18	M	R temporal	Headache → loss of consciousness (LOC) with R or L tonic posturing	Sharp and slow wave complexes R temporal → R frontal → secondary bilateral synchrony Low voltage delta activity R hemisphere	R frontotemporal	—	Unknown	Mental subnormality Higher sensory threshold L side of body
14	13	M	Generalized over scalp	*Déjà vu* → headache → LOC	Excess L temporal theta activity	L temporal	—	Trauma	Impaired fine finger movements L side
15	46	M	R supra-orbital	Headaches → LOC with head and eyes to L → grand mal	Delta focus R occipital-posterior temporal Electrographic seizure R occipital R temporal sharp waves	R occipital-posterior temporal	Sharp, severe	Unknown	None
16	20	F	L temporal → bitemporal	Headache → 'needles over vertex' → automatism	R temporal sharp waves	R temporal	Sharp	?Mesial temporal sclerosis (status epilepticus in childhood)	None
17	12	M	R occipital	Headache → aphasia wavy lines in vision → grand mal	R occipitoparietal spikes	R parietal	Throbbing	?Migraine	None
18	10	M	L frontal	Headache → face pulls to L and then twitches → L arm tonic extension	Delta R hemisphere Multiple independent R hemisphere spikes, maximum frontal-temporal	R central-frontal	—	Head injury	None
19	11	F	Generalized over scalp	Headache → vertigo → sees flashing lights → grand mal	R midtemporal spikes Excess theta and delta activity posteriorly, maximum on L	R temporal	Steady	Perinatal injury	Congenital R hemiparesis

20	37	F	Posterior head	Odd smell → head pain → feels teeth protruding → L side feels heavy → twitching L face and L middle finger	Delta and excess theta activity L temporal	L temporal	—	Unknown	Normal
21	17	F	L supra-orbital	Headache → sick feeling in abdomen → fear → L sided clonic jerking	Sharp waves and R temporal delta activity	R temporal	—	Perinatal injury	Mild mental subnormality

TABLE 3 ABDOMINAL GROUP

Case	*Age (yrs)*	*Sex*	*Site of pain*	*Sequence of ictal events*	*EEG data*	*Definite or probable site of seizure origin*	*Quality of pain*	*Cerebral lesion and aetiology*	*Neurological deficits*
22	18	M	Epigastrium	Epigastric pain → loss of awareness, staring, elevation of R arm	L midtemporal spikes spreading to L central and L posterior temporal	L temporal or L insula	—	Varicella encephalitis(?)	Mild mental subnormality
23	21	M	Epigastrium	Abdominal pain → LOC with automatisms	Multiple independent spikes, maximum R anterior temporal-superior frontal Recorded seizure R anterior midtemporal	R temporal	'Sharp'	Hemiconvulsions in childhood	Dull normal intelligence
24	15	F	Mid-abdomen	Abdominal pain → head sensation → generalized tonic seizure	Multiple independent spikes, maximum L anterior	L temporal	—	Mesial temporal sclerosis(?) following status epilepticus in childhood	Dull normal intelligence

Case 20. This 37-year-old woman developed attacks one year ago, beginning with an olfactory aura, followed by posterior head pain and a sensation of her teeth protruding. Her left side then felt heavy followed by a twitching of the left face and then of the left middle finger. Examination was normal. The EEG showed a slow wave abnormality in the left temporal region. A CT scan was normal. The aetiology remains unknown.

Case 21. This 17-year-old girl had seizures beginning with a left supraorbital headache followed by a 'sick feeling' in the abdomen. She then experienced a feeling of fear followed by left-sided clonic jerking. She was thought to have had a perinatal injury. She was mildly subnormal mentally. The EEG showed sharp waves as well as a nonspecific slow wave abnormality in the right temporal region.

Abdominal Group

There were only 2 males and 1 female in this, the smallest group (Table 3). Ages ranged from 15 to 21 years. In each case the abdominal pain was the first symptom in the ictal sequence. The pain was central epigastric or midabdominal and did not rise. All 3 patients had dull normal or mildly subnormal intelligence.

Case 22. This 18-year-old man suffered varicella encephalitis in early childhood. He was left with seizures beginning with epigastric pain followed by loss of awareness, staring and elevation of the right arm. Apart from mild mental subnormality, there was no neurological deficit. His EEG showed left midtemporal spikes spreading to the left central and left posterior temporal regions.

Case 23. This 21-year-old man had hemiconvulsions in childhood. His seizures subsequently began with a 'sharp' abdominal pain, 'like someone hitting me with an axe', followed by loss of consciousness with automatisms. Apart from dull normal intelligence, there was no neurological deficit. His EEG showed multiple independent spikes, maximal in the right anterior temporal and superior frontal regions. A recorded clinical and electrographic seizure began in the right anterior-midtemporal region.

Case 24. This 15-year-old girl developed convulsive status epilepticus in early childhood. Her subsequent seizures began with abdominal pain followed by a head sensation that was difficult to describe. This progressed to a generalized tonic seizure. She showed dull normal intelligence but no other neurological abnormality. The EEG showed multiple independent spikes, maximally in the left anterior temporal region.

DISCUSSION

Unilateral Seizures

Patients with painful unilateral seizures comprised 1.2 per cent of our epileptic population. This group constituted 23.6 per cent of the 127 patients with somatosensory epilepsy of Mauguière and Courjon (1978) or 0.34 per cent of their total epileptic population of 8939 patients.

In all 10 cases, the site of seizure origin can be lateralized to the cerebral hemisphere contralateral to the pain, based on clinical and EEG data (Table 1). This has been noted by other authors who described painful unilateral seizures (Gowers, 1901; Head and Holmes, 1911; Michelsen, 1943; Lewin and Phillips, 1952; Russell and Whitty, 1953; Whitty, 1953; Fine, 1967; Wilkinson, 1973; Mauguière and Courjon, 1978). In these series the parietal region was the commonest site for lesions responsible for the painful seizures, except for the cases of Mauguière and Courjon (1978) in which somatosensory seizures with pain were more common when the central-parietal region was unaffected. Of our patients, 2 had parietal lesions, 2 had extensive frontoparietal lesions and 2 had lesions involving the rolandic region more than other regions. Others had no demonstrable lesions. The site of the lesion, however, may not always correlate with the site of the seizure during ictal pain, especially if the pain does not occur early in the ictal sequence.

Only in Cases 2 and 10 were the seizures due to progressive lesions. Case 2 had seizures due to chronic focal encephalitis while Case 10 had metastatic melanoma. This is in contrast to the 46.5 per cent prevalence of brain tumours in patients with somatosensory epilepsy described by Mauguière and Courjon (1978). The difference may be due to the higher proportion of children in our series.

Evidence for Rolandic Involvement at the Time of Pain

Clinical features which characterize rolandic involvement by a seizure include a jacksonian motor or sensory march or clonic jerks localized to part of one side of the body. Electrical stimulation of the postcentral gyrus (primary somaesthetic area of SI) may produce tingling, numbness or thermal sensations (Penfield and Jasper, 1954). In 3 patients (Cases 3, 5 and 9), unilateral pain followed paraesthesiae in the same distribution. The paraesthesiae had a 'march' implying contralateral SI involvement. In Case 9 clonic jerks of the hip after the pain also supported involvement of the rolandic region. In Cases 1 and 10 the pain itself showed a unilateral march as the first ictal symptom. In Case 8 left arm pain was immediately followed by a jacksonian motor march of the same limb, implicating the rolandic region.

In Case 2 the initial sensory symptom in the toes of the left foot was followed by a jacksonian motor march from the foot to the calf. Pain occurred during clonic contractions of the calf muscles. Although the contractions might have caused the pain, we have encountered patients with more vigorous muscular contractions during focal seizures who did not find the contractions painful. We thus favour a central origin for the pain. In Case 4 a paraesthetic sensory march preceded tonic then clonic jerks on the same side of the body. Although the pain accompanied the clonic jerks, the pain was more of a dysaesthetic quality, suggesting a sensory mechanism.

In Case 6, initial vocalization was followed by right arm pain which could also be due to a rolandic discharge, as vocalization has been produced with rolandic stimulation (Penfield and Boldrey, 1937; Penfield and Roberts, 1959).

The ictal sequence in Case 7 is complex. The early illusion of movement implied parietal or temporal neocortical involvement. The subsequent tightness in the cheek followed by a painful march to the adjacent mastoid and shoulder area would be compatible with forward spread of the seizure to the rolandic region.

Seizures were recorded on EEG in 5 patients (Cases 1, 5, 6, 7 and 10). They began in the central (rolandic) region contralateral to the pain in Cases 1, 5 and 6. In Cases 1 and 6 pain was the first ictal symptom, so pain occurred with rolandic ictal activity. In Case 1 the epileptiform activity was more precisely localized in the postcentral gyrus at electrocorticography. Interictal epileptiform activity as spikes or sharp waves involved the central region contralateral to the pain in Cases 1, 2, 5 and 6.

Role of the Cerebral Cortex in Pain

SI, the primary sensory area, includes Brodmann's areas 3, 2 and 1 with contralateral body parts represented in the form of a distorted 'homunculus' (Penfield and Jasper, 1954). It receives projections from the ventroposterior thalamic nuclei. In the monkey the SI neurons are sensitive to non-noxious stimuli, touch, pressure and movement of contralateral body parts. A small percentage respond to noxious stimuli over wide receptive fields (Mountcastle and Powell, 1959). However, Mountcastle (1974) points out that much of the representational area for the contralateral skin surface is buried in the posterior bank of the central sulcus, receiving the ascending projection of the neospinothalamic system.

SII, the secondary sensory area, occupies the superior bank of the sylvian fissure, extending from the inferior portion of the precentral gyrus to the inferior anterior parietal region (Penfield and Jasper, 1954; Carpenter, 1976). Although there is bilateral representation of body parts, the contralateral side predominates. The face area has not yet been verified in man, but SII merges with the lower rolandic region in what should be the 'face area' (Penfield and Jasper, 1954). SII may play a role in pain perception as it receives projections from the posterior group of thalamic nuclei which in turn receive fibres from the spinothalamic system. Some neurons in SII are sensitive only to noxious stimuli (Poggio and Mountcastle, 1960). Reciprocal connections exist between SI and SII. Each also has connections with the motor cortex of the same cerebral hemisphere in the rhesus monkey (Jones and Powell, 1969).

Penfield and Boldrey (1937), stimulating the exposed brains of humans under local anaesthesia, elicited painful sensations referred to body parts other than the head in only 11 of over 800 responses. That unilateral pain was produced is significant. Its rarity may partly relate to a large part of the skin surface representational area lying in the central sulcus (Mountcastle, 1974). Bindman and Lippold (1981) also suggested that electrical stimulation of the cortex produces an 'unnatural pattern of excited cells' and that certain spatial arrangements of excited neurons may be required for pain to be perceived.

Chatrian *et al.* (1975), working with humans, recorded a cortical evoked response in the lower postcentral regions contralateral to tooth pulp stimulation. Such stimulation affects A delta and C fibres which mediate pain sensibility.

Clinical experience has also shown a possible cortical role in pain sensibility. Marshall (1951) reported several cases of traumatic cortical injuries not directly involving the thalamus, with loss of pain sensation localized to a contralateral body part. This analgesia often had an abrupt demarcation, as in our Case 1. Lewin and Phillips (1952) successfully relieved painful seizures in 1 patient and local limb pain in 2 other patients with resection of the contralateral postcentral gyrus. Biemond (1956) reported a case of severe central pain with infarction in the region now known as SII. Others have reported cortical lesions with a variety of alterations in pain sensation ranging from analgesia to hyperpathia (Russell, 1945; Sinclair, 1967; Lende *et al.*, 1971).

Possible Mechanism for Painful Unilateral Seizures

In our patients with unilateral painful seizures clinical and electrographic data implicate ictal involvement of the rolandic region, contralateral to the pain, at the time of the painful portion of the seizure. Seizures in some patients began in areas other than the rolandic region, but probably spread to this region at the time of the pain. In most cases this appeared to be due to involvement of SI. We cannot, however, conclude that pain was 'perceived' in the SI area as spread to the SII or the thalamus (Dusser de Barenne and McCulloch, 1938; Prince and Schwartzkroin, 1978), could also have occurred. Furthermore, as Melzack and Wall (1968) point out, there is probably no single 'pain centre', as various parts of the brain (limbic system, hypothalamus, and other sites) are involved in pain perception and the response to the sensation of pain.

Inhibitory mechanisms have been shown to be important in the control of pain, and it is likely that this applies to all levels of the neuraxis (Kerr and Wilson, 1978). It is known that in the generation of seizures there is depression or elimination of inhibitory mechanisms (Ajmone-Marsan and Gumnit, 1974). It is possible that the decreased inhibition accompanying a seizure interferes with pain control mechanisms in certain cortical areas. This may account for the apparent intensification of paraesthetic or dysaesthetic sensations to the point of becoming painful as in some of our patients.

Cephalic Group

Patients with cephalic ictal pain made up 1.3 per cent of our patients with epilepsy. In Gowers' (1901) series of 1450 epileptic patients, 50 had cephalic auras and 21 (1.4 per cent of his total population) had cephalic ictal pain.

Like Penfield and Jasper (1954), we found cephalic pain to have 'little localizing value' for the site of seizure origin. In 7 of the 11 patients, pain was the initial symptom of the ictal sequence (Cases 13, 15–19 and 21). Headache was lateralized in all of these except Case 19. As can be seen from Table 2 there was no consistent relationship between the site of seizure origin and the site of head pain when the pain was the initial symptom. It was on the same side in 3 cases (13, 15 and 17) and lay over the site of seizure origin in 2 (Cases 13 and 17). In 2 (Cases 18 and 21), the headache was contralateral to the site of the seizure origin and in Case 19 generalized head pain was associated with a right temporal lobe origin for the seizures.

In the remaining cases (11, 12, 14 and 20), headache followed other ictal symptoms. In 3 (Cases 12, 14 and 20), the headache was bilateral while in Case 12 the headache was on the side of the cerebral seizure.

In 8 of the 11 cases the temporal lobe was involved in the seizure, probably reflecting the high prevalence of temporal lobe seizures among those epileptic patients with focally arising seizures.

Two patients (Cases 11 and 17) described the pain as throbbing, suggesting a vascular component. Others described a steady or sharp quality to the pain or ascribed no quality to it. No patients were encountered with a dysaesthetic quality to the pain, as in the Unilateral Group.

In terms of aetiology, Cases 11, 19 and 21 probably had a perinatal insult as the cause of their epilepsy. Trauma was the likely cause in Cases 14 and 18. Case 16 may have had mesial temporal sclerosis from status epilepticus in childhood resulting in later psychomotor seizures. Case 17 had recurrent headaches with speech problems and bright wavy lines in the visual fields, the latter reminiscent of the visual phenomena described by migrainous subjects. His attacks could well have been considered to be migraine, but one progressed to a grand mal convulsion. He was the only subject who had probable migraine. In none of our subjects was a progressive lesion encountered. No patients were found to have arteriovenous malformations.

The mechanism of the production of headache may differ from one patient to another. In Case 18, the only case with possible rolandic involvement by the seizure, left frontal head pain at the onset of the seizure correlated with interictal right central-frontal epileptiform activity on EEG. Since the scalp does have representation in the rolandic region, it is possible that in this case ictal pain could have been produced by a mechanism similar to that for the Unilateral Group. It is unlikely, however, that cephalic pain was produced by rolandic involvement in the other Cephalic Group patients.

As mentioned, Case 17 may have had migraine accounting for headaches and seizures. Spreading cortical depression has been invoked to explain the slow march of neurological symptoms and also the evolution of seizures during migraine (Basser, 1969; Camfield *et al.*, 1978). Camfield *et al.* (1978) described 4 adolescents with 'severe epileptiform' EEG abnormalities and basilar migraine who developed epileptic seizures triggered by attacks of migraine.

It is more difficult to explain the causation of headache in our other patients. Possible mechanisms include muscle contraction, traction, and vascular, inflammatory and 'neuralgic' factors (Lance, 1978; Dalessio, 1980). Of these a vascular mechanism seems the most attractive. It has been shown by Plum *et al.* (1968) that cerebral blood flow rises two to fourfold with a rise in respiratory quotient to 1.45 in paralysed, ventilated animals during pentylenetetrazole induced seizures. Penfield and Jasper (1954) also noted increased cerebral blood flow during seizures, with loss of pulsation in pial arteries which they deduced was due to 'decreased resistance' to flow. Such loss of autoregulation would probably affect mainly the pain-insensitive pial arteries Mchedlishvili, 1980) rather than more proximal segments of anterior, middle and posterior cerebral arteries which are sensitive to pain (Ray and Wolff, 1940). It is possible, however, that dilatation of these more proximal vessels might also occur. This must be uncommon as cephalic pain is infrequently reported as a feature of the seizure itself.

'Seizure headaches' (Swaiman and Frank, 1978) or 'epileptic cephalea' (Halpern and Bental, 1958) are terms applied to a syndrome in children, consisting of headache, epileptiform activity on EEG and the prevention of headaches by anticonvulsants. Jonas (1966) described a similar syndrome in adults. Swaiman and Frank (1978) proposed that the headaches are due to seizures causing an autonomic discharge which is turn causes altered blood vessel tone and vascular headache. The success of anticonvulsant therapy in preventing the headaches is not necessarily proof that the headaches are due to seizures, as Camfield *et al.* (1978) have observed that anticonvulsants may prevent migraine attacks. Also epileptiform activity on EEG may sometimes be seen in migraine subjects.

Abdominal Group

Of our epileptic patients 3 (0.4 per cent) had painful abdominal auras. In Gowers' (1901) series of 1450 patients it was more common, occurring in 1.17 per cent of his epileptic patients.

In our 3 cases the clinical and EEG features pointed to a temporal lobe origin for the seizures. This was most convincing in Case 23 in whom a clinical seizure recorded on EEG began in the right anterior-midtemporal region. Although the EEG data favoured a temporal lobe origin for the seizures in Case 22, the clinical features of the attacks would be compatible with supplementary motor seizures.

Gowers (1901) noted that when the initial abdominal sensation was actual pain, it remained in the epigastrium until consciousness was lost. He noted it was almost always central or just to the left of the midline. These features applied to our 3 cases.

'Abdominal epilepsy' has been defined as a syndrome of paroxysmal abdominal pain associated with altered awareness, EEG abnormalities and a good response to anticonvulsant medication (Douglas and White, 1971). The condition has been reported mainly in children and young adolescents. In Douglas and White's (1971) 5 children, 3 had generalized spike and wave activity on EEG suggestive of a primary generalized type of seizure disorder and 2 had temporal lobe spikes. All 4 adult cases reported by Peppercorn *et al.* (1978) had temporal lobe seizures.

Penfield and Kristensen (1951) found that when the thoracic or abdominal aura occurred as the first ictal symptom in focal seizures, as in our 3 patients, the origin was either deep within the sylvian fissure or 'intermediate frontal', especially in the supplementary motor area.

Of Van Buren's (1963) 100 patients with 'abdominal aurae', 69 had temporal lobe seizures. Others had seizure origins in either the frontoparietal, central or occipital lobes or the supplementary motor area. Three had *petit mal* seizures. With his stimulation experiments, the epigastric aura could be produced by stimulation of the insula, basal ganglia or mesial temporal region. In addition to the above sites, Ajmone-Marsan and Ralston (1957) noted that the epigastric aura could be produced by stimulation or ictal involvement of the inferior surface of the frontal lobe.

It is not clear how abdominal pain is actually produced. In Van Buren's (1963) series, the abdominal aura was rarely accompanied by peristaltic activity in the gastrointestinal tract. Eight of his 100 patients had painful epigastric auras and none of these had evidence of excessive peristalsis. Downman (1951), using cats and dogs, found that electrical stimulation of the splanchnic nerve or mechanical stimulation of the mesentery caused evoked responses in the contralateral SI or bilateral SII areas. There was no associated body wall movement. Amassian (1951) found splanchnic responses in the trunk region of the postcentral gyrus in the monkey, even under deep anaesthesia. At lighter anaesthetic levels, cortical responses were also detected in precentral and posterior parietal areas and, with longer latency, from the ipsilateral postcentral region. Activation of A delta and gamma fibres in the splanchnic nerves of the cat produces a response in contralateral SI after a long (30 ms) latency (Langhof and Rubia, 1969).

From stimulation of the cerebral cortex and from evoked responses of splanchnic nerve stimulation, it would appear that abdominal sensation (including pain) can be produced by activation of certain areas of the cerebral cortex without the need to involve a peripheral mechanism. In clinical cases described in the literature, there is little evidence of involvement of the rolandic region during the epigastric aura. Involvement of other regions such as SII or the supplementary motor area seems more likely, but other areas apparently may also be involved, particularly the temporal lobe and its connections.

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OCULAR MOTOR DEFICITS IN PARKINSON'S DISEASE

I. THE HORIZONTAL VESTIBULO-OCULAR REFLEX AND ITS REGULATION

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SUMMARY

Horizontal vestibulo-ocular reflex (VOR) function was quantified in 14 parkinsonian patients and compared with that of 10 age-matched normals. Eight patients had mild and 6 had advanced rigidity and akinesia. In advanced disease VOR gains were subnormal in darkness during sinusoidal whole-body rotation at frequencies from 0.3 to 3.0 Hz. When fixating a stationary target, patients enhanced VOR gains to near unity, but gains of patients with advanced disease were significantly lower than controls. Visual suppression of the VOR by fixating a target moving with the head was defective in all stages of the disease. Advanced patients also exhibited defective voluntary control of the reflex in darkness: both voluntary enhancement, by imagining a stationary target, and voluntary suppression, by imagining a target moving with the head, were abnormal. This disordered voluntary control of the VOR was independent of defective visually mediated smooth pursuit.

Attempted visual and voluntary suppression of the reflex produced a rise in VOR gain, above the hypoactive values recorded in darkness in advanced disease. This inappropriate activation of the VOR implied structural integrity of brainstem smooth eye movement pathways, despite vestibulo-ocular hyporeflexia. Unrecognized degeneration in brainstem VOR circuits, or defective cerebral hemisphere control of the reflex caused by the nigrostriatal or cerebral cortical dysfunction of Parkinson's disease, may explain subnormal ocular responses to passive head motion. We attribute the abnormal visual and voluntary modulation of smooth eye movements to disordered long-loop cerebral control of the VOR and suggest that it is analogous to the defective long-loop cerebral regulation of spinal reflexes that occurs in Parkinson's disease.

INTRODUCTION

Dysfunction of the saccadic, pursuit and vergence systems of ocular motor control is common in Parkinson's disease (Corin *et al.*, 1972; DeJong and Melvill Jones, 971; Shibasaki *et al.*, 1979). Despite the frequent occurrence of disordered postural reflexes to whole body motion (McDowell *et al.*, 1978), no abnormality of ocular reflexes to head motion has been recognized (Teräväinen and Calne, 1980).

The vestibulo-ocular reflex (VOR) subserves vision during head movement by stabilizing the eyes relative to the visual environment. For clear perception of

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stationary targets, the ratio of smooth eye movement velocity to head velocity (VOR gain) must approximate unity. However, in the absence of vision, VOR gain is less than one during head motion at frequencies below 1.0 Hz. Vision is used for augmentation of the VOR when viewing stationary targets. For clear perception of moving targets, while tracking with the head, the VOR must be suppressed. Vision is required to suppress the VOR gain to near zero so that the eyes remain stable in the orbit. This modulation of the VOR stabilizes the target image near the fovea. Normal subjects can also voluntarily enhance their VOR without visual aid by imagining a stationary target, and suppress it by imagining a target moving with the head (Barr *et al.*, 1976). We report the study of the horizontal VOR and its visual and voluntary (nonvisual) control in Parkinson's disease.

METHODS AND SUBJECTS

Fourteen patients with parkinsonism, 13 with idiopathic Parkinson's disease and one patient with a posthypoxic parkinsonian syndrome (age range 39 to 74 years, mean 54; 7 women), were examined and compared with 10 normal subjects (age range 40 to 63 years, mean 51; 6 women). All patients underwent full neurological examination by the senior author prior to oculomotor recordings. Known duration of disease was recorded. The major signs of tremor, rigidity and bradykinesia were graded on a scale of 0 to 3, with 0 being absence of abnormality and 3 most severe. Consistency of evaluation was established by comparing examination findings with the assessment of an independent neurologist using the same criteria.

We selected patients without clinical evidence of dementia. Tests of intellectual function included orientation in time and person, immediate, short, and long-term memory, ability to calculate, interpretation of proverbs, and spatial orientation. After ocular motor testing, neuropsychological evaluation by the verbal section of the Wechsler adult intelligence scale (WAIS, revised) was performed in 6 patients, 4 with advanced disease (Cases 1, 2, 3 and 4; Table 1) and 2 with mild parkinsonism (Cases 9 and 10). This test confirmed absence of global dementia. IQ scores ranged from 103 to 126 in the 6 patients and were consistent with their education and occupational backgrounds. One patient was a clinical psychologist, so familiar with the WAIS that his high performance was unreliable. He scored highly with two unfamiliar tests, the Wisconsin card sort test (10 categories) and item 99 from the Luria-Nebraska battery (score 7/8).

Horizontal eye movements were simultaneously recorded by infrared oculography and d.c. electro-oculography (EOG). We monitored blink artefacts using skin electrodes above and below one eye. Data were stored on magnetic tape for off-line digitization and analysis using a LSI 11 microprocessor. Analogue signals of eye and chair position were also displayed on an ink jet writing polygraph (Mingograph 1600). Infrared recordings were used for quantitative analysis; this system remained linear over a 20 deg range from midposition. After digitization at 200 samples/s, the full system bandwidth was 0 to 100 Hz. Resolution was 15 min of arc with an accuracy of ±1 deg.

Low Frequency Oscillation

Subjects were seated in a vestibular chair, permitting horizontal whole body rotation in the yaw axis, with the head stabilized by occipital, parietal, frontal and chin supports. Targets were either a single light-emitting diode placed 114 cm from the nasion of the subject, or a laser projected from the rear on to a screen 170 cm from the nasion. Eye movement calibrations were performed before and following each protocol. Chair (head) position was measured using a precision quality potentiometer (Vernitech) giving linear output throughout the complete range of chair excursion. Chair calibration remained stable throughout the recording period. For all vestibular paradigms, the chair was oscillated manually through 20 ± 2 deg at frequencies averaging 0.3, 0.5 and 1.0 Hz. Peak chair velocities at each frequency were 19 ± 4, 31 ± 6 and 63 ± 12 deg/s, respectively.

Subjects were oscillated under 5 conditions which assessed the VOR, first without any instruction which actively stimulated subjects to modulate their VOR, and subsequently, with instructions which induced visual and voluntary (nonvisual) regulation of the VOR. (1) *Darkness:* subjects were oscillated in darkness while performing mental arithmetic to maintain alertness. (2) *Visible stationary target.* subjects were asked to fixate an earth-fixed target. (3) *Imagined stationary target:* this was as in condition (2), but with the visible target replaced by an instruction to imagine a stationary target in darkness. (4) *Visible moving target:* subjects were oscillated while fixating a laser target electronically coupled with the chair so that it moved in synchrony with the head. (5) *Imagined moving target·* this was as in condition 4, but with the visible target replaced by an instruction to imagine a target moving with the head in darkness.

High Frequency Oscillation

Four patients, 3 with advanced disease and one mildly impaired, were placed in a hydraulically driven, computer controlled vestibular chair and subjected to whole body sinusoidal oscillation in darkness, at 1.0, 2.0 and 3.0 Hz, while performing mental arithmetic. Peak chair velocity approximated 55 deg/s at all frequencies. Eye movements were recorded by EOG (d.c.-100 Hz) and the data stored on floppy disc for later analysis. Chair (head) position was measured by a precision quality potentiometer and velocity obtained by differentiation of the signal.

Data from the low frequency experiments were edited on a graphics terminal prior to analysis. Cursors were placed at the zero velocity points on the chair position trace. This permitted accurate assessment of the chair (head) frequency. A segment of chair movement, at peak velocity, was demarcated and a time-locked segment of the eye movement recording, free of blink or other artefact, was similarly marked. Velocity segments ($20 < n < 30$) were analysed at each frequency for each subject. Frequency of oscillation was calculated as the mean frequency of individual events. VOR gains were calculated as eye velocity divided by chair velocity. Mean VOR gain was calculated at each frequency. Digitized signals from the high frequency experiments were also displayed on a screen, saccades were edited out, and the remaining smooth eye movements were treated with a low-pass filter at 5 Hz. A sinusoidal eye position trace was reconstructed and then differentiated to a velocity trace. VOR gain was computed for each half sinusoid of displacement. Statistical analyses of results from each paradigm were performed using the nonparametric Mann-Whitney U test.

RESULTS

Patient Evaluation

Two patient groups were identified on the basis of known duration of illness and the severity of rigidity and akinesia (Table 1). These groups were designated as mild or advanced. A score of 2 or more for any individual major symptom plus a duration of disease greater than five years, or a score of 2 or more for at least two of the major symptoms, resulted in a patient being classified as advanced. No patient was severely disabled with regard to daily life and none was demented. All patients in the group with advanced disease had impaired postural reflexes as evidenced by a tendency to fall when turning or hurrying. All subjects had normal auditory acuity to clinical testing. All but 3 patients were taking L-dihydroxyphenylalanine (L-DOPA) with or without a peripheral decarboxylase inhibitor. Five of 14 patients were receiving anticholinergic medication (Table 1).

TABLE 1 SUMMARY OF PATIENTS

Patients	*Age (yrs)*	*Sex*	*Duration of illness (yrs)*	*Treatment*	*Symptoms* *Rigidity*	*Bradykinesia*	*Tremor*
Advanced							
1	40	M	12	L-DOPA Orphenadrine Baclofen	3	2	0
2	58	F	19	L-DOPA Trihexiphenidyl	2	2	2
3	63	M	9	L-DOPA Benztropine Amantadine	2	3	0
4	52	F	2	Amantadine Trihexiphenidyl	2	2	2
5	50	F	12	L-DOPA	3	3	0
6	74	M	7	—	2	2	0
Mildly impaired							
7	39	M	4	L-DOPA Cogentin Benztropine	1	2	0
8	67	F	3	L-DOPA	0	1	0
9	59	M	1	L-DOPA Trihexiphenidyl	0	1	2
10	57	F	2	—	1	2	0
11	67	M	3	L-DOPA	0	3	2
12	44	M	6	—	1	1	1
13	58	F	13	L-DOPA	1	1	2
14	51	F	2	L-DOPA	0	1	0

No patient complained of vertigo or visual disturbance. Uncorrected binocular visual acuity was 20/40 or better in all subjects. Studies were performed without correction. None of the patients exhibited spontaneous nystagmus. Other ocular motor findings included saccadic pursuit and multistep hypometric saccades (White *et al.*, 1983). Case 6 had an old left frontal thromboembolic infarct without clinical residua, and Case 2 had had a stereotactic lesion in the left thalamus ten years earlier. Neither patient differed significantly from the others in their group. Case 5 had typical parkinsonism following a period of prolonged hypoxia; a CT scan was normal and electrophysiological testing showed long-latency reflex abnormalities characteristic of parkinsonism (Tatton and Lee, 1975).

1. *Darkness.* Mean VOR gains of the control group ranged from 0.68 at 0.3 Hz to 0.97 at 1.0 Hz (Table 2), consistent with VOR gains of subjects of undefined age (Barr *et al.*, 1976) and with those of younger normal subjects (Sharpe *et al.*, 1981). Mildly affected patients had normal VOR gains. Patients with advanced disease had subnormal VOR gains at all frequencies ($P < 0.01$; Table 2; fig. 1A). These patients had prolonged periods of wandering eye movements, independent of vestibular influence, at frequencies of oscillation less than 2 Hz (fig. 1B).

2. *Visible stationary target.* All subjects were able to increase VOR gain to near unity at all frequencies (Table 2). Although each patient with advanced disease had a

TABLE 2. VESTIBULO-OCULAR REFLEX (VOR) GAIN

		Patients	
Frequency (Hz)	*Controls (n = 10)*	*Mild (n = 8)*	*Advanced (n = 6)*
VOR—Darkness and mental arithmetic			
0.3	0.68±0.16	0.75±0.29	0.20±0.18***
0.5	0.76±0.19	0.78±0.29	0.20±0.21***
1.0	0.97±0.13	0.99±0.17	0.50±0.30***
VOR—Visible stationary target			
0.3	1.06±0.08	1.13±0.13	0.86±0.15**
0.5	1.09±0.10	1.17±0.17	0.90±0.20
1.0	1.12±0.09	1.15±0.18	0.95±0.04***
VOR—Imagined stationary target			
0.3	0.83±0.12	0.81±0.15	0.30±0.11**
0.5	0.95±0.08	1.04±0.24	0.50±0.33*
1.0	1.04±0.10	0.96±0.18	0.65±0.10**
VOR—Visible moving target			
0.3	0.09±0.08	0.20±0.13*	0.32±0.16**
0.5	0.13±0.10	0.32±0.13**	0.36±0.18*
1.0	0.35±0.16	0.66±0.21**	0.62±0.20**
VOR—Imagined moving target			
		(n = 4)	(n = 3)
0.3	0.72±0.11	0.63±0.14	0.33±0.14
0.5	0.79±0.06	0.77±0.05	0.18±0.02
1.0	0.89±0.05	1.02±0.23	0.60±0.11

n = No. of subjects. Gain values are the means of the mean VOR gain values for individuals. All P values are derived by the Mann-Whitney U test using the mean VOR gain values of individual subjects. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

mean VOR gain within the normal range (control mean ± 2 SD), comparison of the group results showed that the mean VOR gains of the group were significantly lower than those of controls (Table 2). Standard deviations, derived from the pooling of all data points for all advanced patients, were more than double those of normal VOR gain. The large standard deviation indicated greater variability of performance for each individual event and evidenced considerable retinal image slip (fig. 2). Despite these retinal velocity errors, patients did not complain of visual blurring.

To stabilize the retinal image of a stationary target, the eyes must have a compensatory phase lag of 180 deg relative to the head. Such phase lag is, by convention, defined as zero. Phase lag indicates that the eyes lag behind the head while phase lead indicates that the eyes lead the head. If the VOR phase difference is

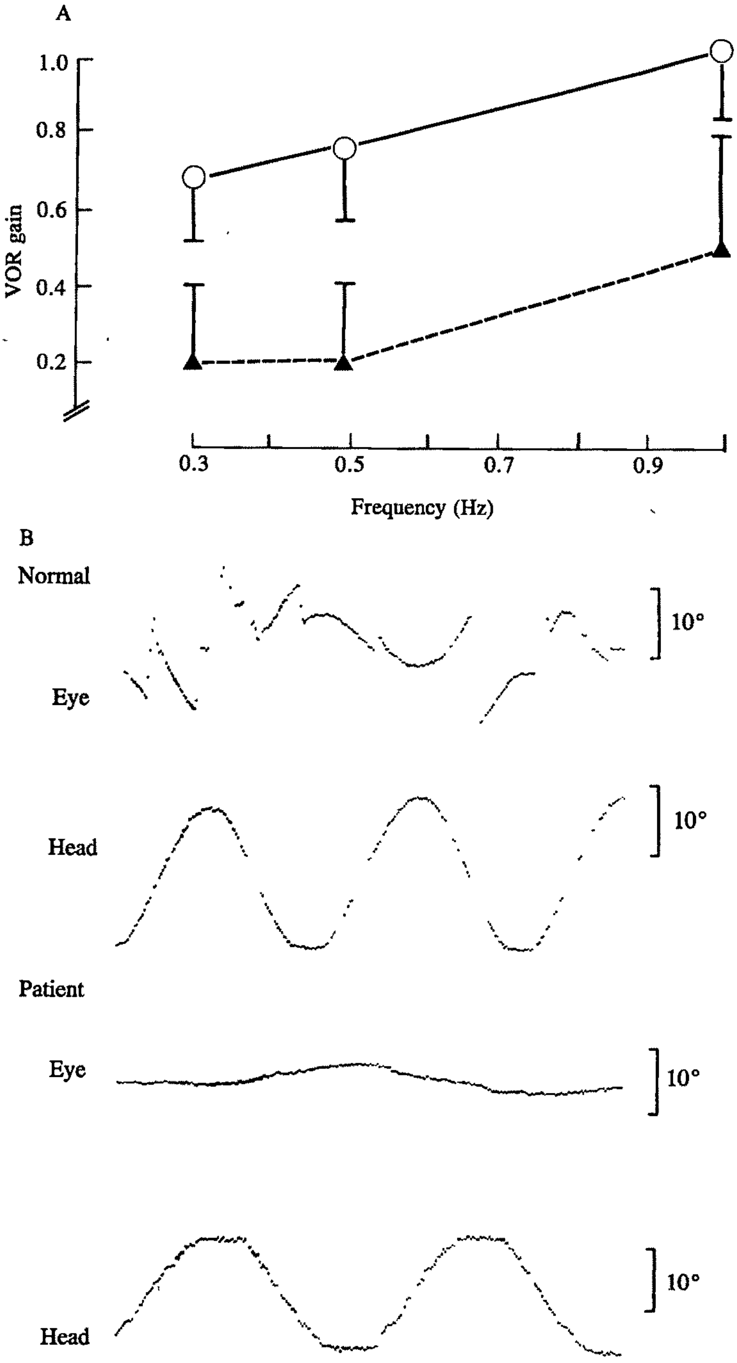

FIG. 1A, graphs of mean VOR gains in darkness at 3 rotational frequencies. Patients with advanced disease (▲). Normal subjects (○). Error bars represent 1 SD. B, examples of digitized horizontal eye and head position, recorded in darkness, in a normal subject and a patient with advanced disease. Right is upward, left downward.

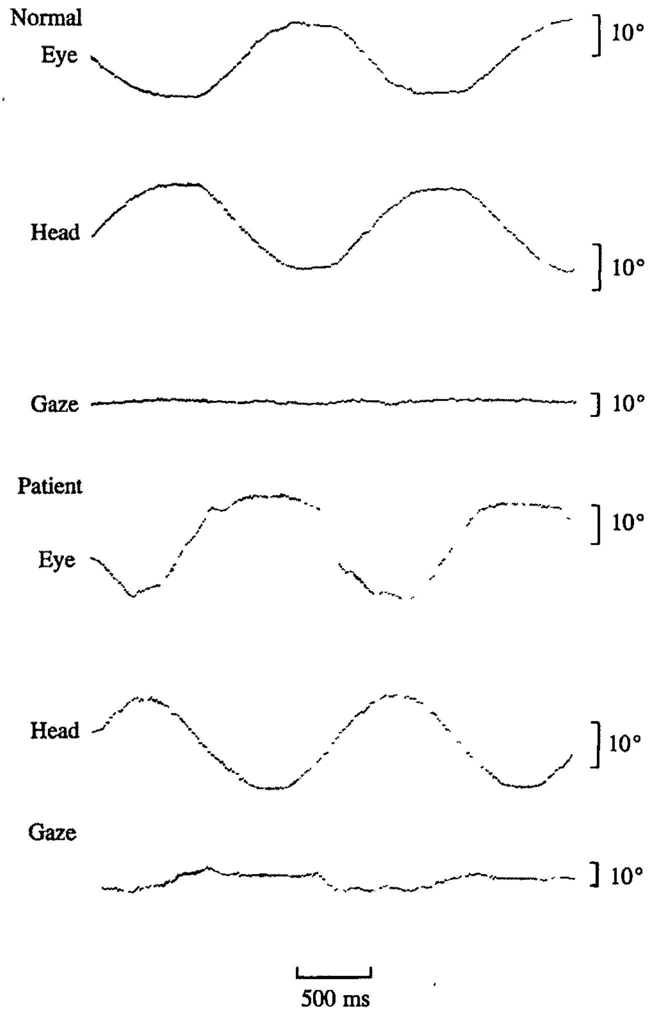

FIG. 2. Recordings of horizontal eye, head and gaze (eye plus head) positions obtained while subjects fixated a stationary target. Gaze channels show retinal image motion in patient compared with normal subject. Right is upward, left downward.

too large, the image is never stationary on the retina. The VOR phase was measured for oscillation with a visible stationary target. In other conditions the low and variable gains precluded reliable phase measurements. Normal subjects had a slight phase lead (mean under 1.0 deg). Mildly affected patients showed a normal VOR phase relationship. Patients with advanced disease had mean VOR phase lags of 4 to 13 deg and much greater variability than normal.

3. *Imagined stationary target.* Normal subjects and mildly impaired patients could elevate VOR gain to near unity. Advanced patients, while able to raise their VOR gain above levels recorded in darkness, were not able to raise it to normal

levels; this defect was significant at all frequencies ($P < 0.05$; Table 2, fig. 3). Furthermore, during this paradigm, patients with more advanced disease had prolonged periods of wandering eye movements without saccades towards the imagined target position.

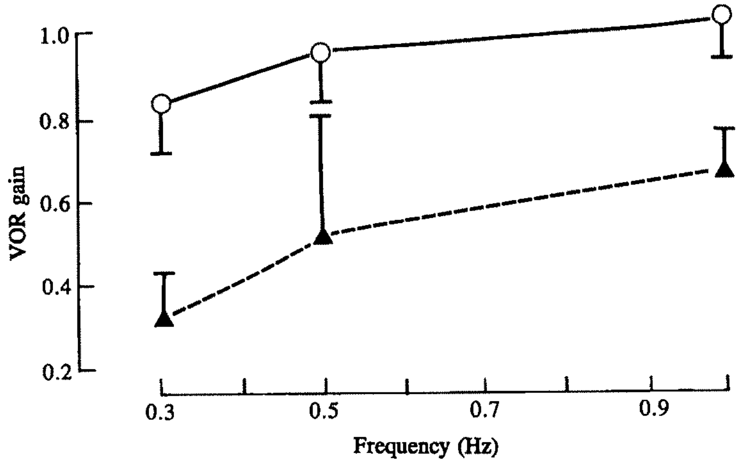

FIG. 3. Graph of mean VOR gains in darkness while subjects attempted to fixate an imagined stationary target. Patients with advanced disease (▲). Normal subjects (○). Error bars represent 1 SD.

4. *Visible moving target.* Normal subjects suppressed their VOR gains to near zero at 0.3 and 0.5 Hz, and to 0.35 at 1.0 Hz. Patients, however, did not decrease VOR gains effectively ($P < 0.05$; Table 2, fig. 4). This deficit was quantified by a VOR suppression quotient obtained by dividing the VOR gain, while attempting to follow a moving target, by the VOR gain in darkness (Table 3). Paradoxically, while attempting suppression, advanced patients actually increased their VOR gains above those levels recorded in darkness ($P < 0.05$; Table 2). This effect is expressed by the high suppression quotients for the group (Table 3).

5. *Imagined moving target.* Four normal subjects and 7 patients were examined. Sustained suppression without a visible target proved difficult for both normal

TABLE 3. VESTIBULO-OCULAR REFLEX (VOR) SUPPRESSION QUOTIENT

Frequency (Hz)	*Controls*	*Patients*	
		Mild	*Advanced*
0.3	0.13	0.27	1.6
0.5	0.17	0.41	1.8
1.0	0.36	0.67	1.24

VOR suppression quotient is the ratio of VOR gain while fixating a moving target to the VOR gain in darkness.

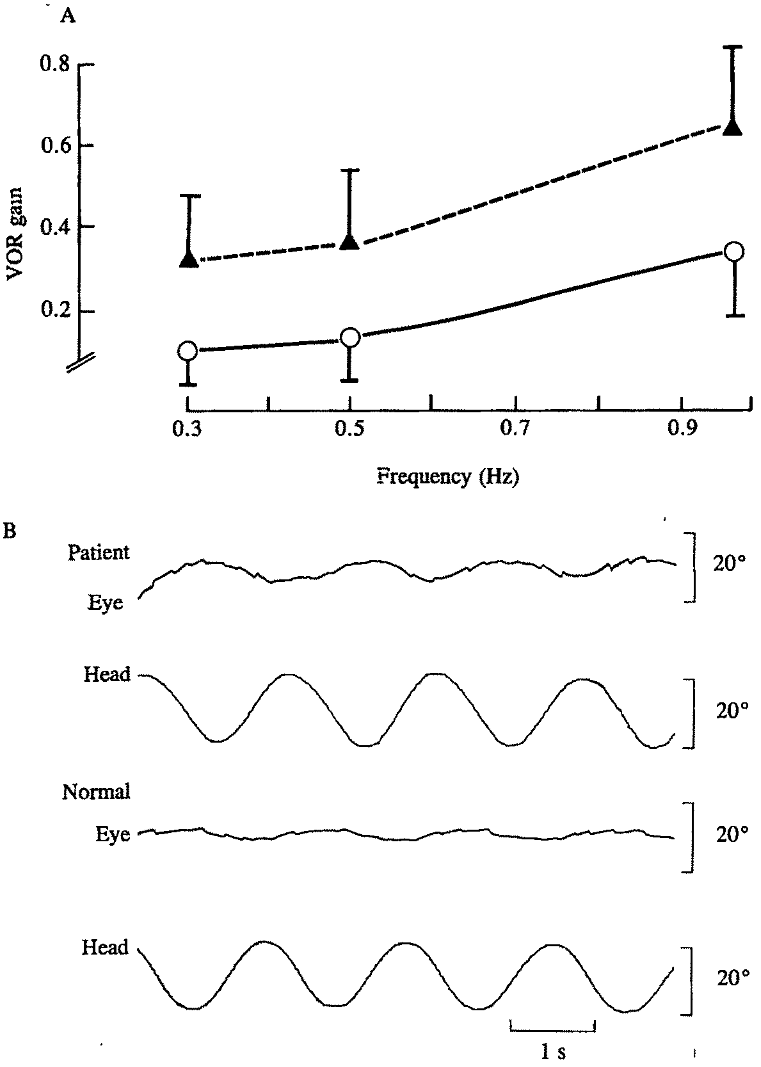

FIG. 4A, graph of mean VOR gains obtained while subjects attempted to suppress their VOR by fixating a target moving with their heads. Patients with advanced disease (▲). Normal subjects (o). Error bars indicate 1 SD. B, examples of eye and head position recorded during attempted visual suppression of VOR in a normal subject and a patient with mild Parkinson's disease. Nystagmus fast phases are evidence of incomplete suppression (*first and third traces*). Vestibular smooth eye movement (slow phase) velocities are higher in patient.

subjects and patients. Normal subjects achieved periods of suppression. More advanced patients failed to suppress their VOR and, indeed, recorded a higher VOR gain than when being oscillated in darkness while performing mental arithmetic (Table 2). Interspersed with their VOR were periods of wandering eye movements, without vestibular smooth eye movements or corrective quick phases.

Polygraph records from 4 patients during rotation in darkness (conditions 1, 3 and 5), showed a consistent unidirectional horizontal drift of the eyes indicating a directional asymmetry of VOR gain. When patients sat motionless in darkness, drift of the eyes was bidirectional and, as in normal subjects, did not exceed 3 deg/s. There was no relationship between the dynamic asymmetry of the VOR and asymmetry of other physical findings.

High frequency oscillation. During oscillation in darkness at 2.0 Hz, the mildly impaired patient had a VOR gain near unity, but at 3.0 Hz, VOR gain increased to 1.4. A similar rise of VOR gain above unity has been recorded in normal subjects oscillated at frequencies between 4 and 5 Hz (Benson, 1970). Patients with advanced disease had subnormal VOR gains even at these higher frequencies (Table 4).

TABLE 4. VESTIBULO-OCULAR REFLEX GAIN DURING HIGH FREQUENCY OSCILLATION IN DARKNESS

	Frequency (Hz)				
Patients	0.3	0.5	1.0	2.0	3.0
Advanced patients					
2	0.31	0.62	0.78	0.9	1.0
4	0.53	0.51	0.48	0.6	0.9
5	0.22	0.65	0.85	0.6	0.9
Mildly impaired patient					
12	0.75	0.65	1.1	1.1	1.4

DISCUSSION

This study documents distinctive disorders of the VOR in Parkinson's disease. As the disease advances, patients demonstrate subnormal horizontal vestibulo-ocular activity during head motion at frequencies ranging from 0.3 to 3.0 Hz. Peripheral vestibular lesions or focal damage in the pontine tegmentum abolish or reduce the reflex by disrupting its three-neuron arc from the labyrinth to ocular muscles (Kasai and Zee, 1978; Cohen *et al.*, 1968). Low gains also occur in some patients with cerebellar system degenerations and have been attributed to vestibular nerve or nuclear atrophy (Baloh *et al.*, 1975). Reichert *et al.* (1982) recorded reduced or absent caloric vestibular responses in a majority of their parkinsonian patients. However, the observed pathology in Parkinson's disease is primarily within nigrostriatal dopaminergic pathways, and no morphological change in the brainstem vestibulo-ocular reflex arc has been recognized (Alvord *et al.*, 1974).

The lack of histological change in the brainstem suggests that the low VOR gains are caused by an unrecognized disorder of synaptic transmission within the arc, or by disordered supranuclear regulation. VOR gains may be reduced by inattention (Collins, 1963). Our patients were instructed to maintain alertness by mental arithmetic. Dementia can be a feature of advancing Parkinson's disease (Lieberman *et al.*, 1979). We selected patients without clinical evidence of dementia, confirmed by psychometric tests, even in advanced disease. Although subtle defects in vigilance or cognition might contribute to subnormal VOR gains in darkness, defective supranuclear control of the three-neuron vestibular reflex arc may be a motor defect, analogous to defective suprasegmental control of the spinal reflex arc in Parkinson's disease.

Supranuclear regulation of the VOR is largely achieved by vision. Continuous modulation and long-term adaptation of the VOR is dependent on visual-vestibular interaction. For example, reversal of retinal image slip gradually attenuates VOR gain to zero (Melvill Jones and Gonshor, 1976). Although the cerebellar flocculus has an established role as a visual relay for such visual adaptation (Robinson, 1976), neither the flocculus nor the three-neuron reflex arc is the site of this physiological plasticity (Miles and Lisberger, 1981). Elevated VOR gain occurs in cerebellar system disease (Baloh *et al.*, 1981). Gresty *et al.* (1977) attributed VOR phase lags at high frequencies to cerebellar dysfunction. These gain and phase changes exemplify pathological change in the reflex. Such cerebellar effects may result from disordered control of a variable gain element acting on the neural integrator which transduces head velocity to eye position (Demer, 1981).

The cerebral hemispheres exert visual, voluntary (nonvisual) and tonic control over the VOR (Sharpe and Lo, 1981). Schiller *et al.* (1980) reported decreased ocular deviation to vestibular stimulation after combined ablation of the frontal eye fields and superior colliculi. In decerebrate cats, Carpenter (1972) found a severe reduction in VOR gain after cerebellectomy. This VOR hypoactivity depends on loss of the cerebral hemispheres since cerebellectomy alone does not have this effect (Robinson, 1976). Acute unilateral cerebral lesions may transiently abolish the contralateral VOR and chronic extensive cortical lesions cause asymmetry of this reflex in both man and the monkey (Pasik *et al.*, 1960; Sharpe, 1982); the asymmetry is increased by attempted visual and voluntary modulation of the VOR (Sharpe and Lo, 1981). Disordered voluntary and visual modulation of the VOR was evident in our patients.

Visual-vestibular Interaction

All patients were able to augment their VOR to gains near unity by fixating a stationary target. Patients with advanced disease, while performing within the normal range, had VOR gains significantly lower than controls. Visual enhancement of the VOR may be mediated by the smooth pursuit system. The mild but significant impairment of visual enhancement of the VOR in Parkinson's disease may be explained by the defective smooth pursuit recorded in these patients (White *et al.*, 1983). Retinal image velocities commonly reached 15 deg/s at 1.0 Hz. Despite this retinal slip, patients did not experience blurring of the stationary target. Dynamic visual acuity declines with increasing retinal error, and the decline correlates with the failure of smooth eye movement to match target velocity (Brown, 1972). We did not measure visual acuity during head motion, but such retinal errors might degrade visual acuity in Parkinson's disease.

Impaired visual suppression of the VOR was recorded in our patients, a defect previously observed in parkinsonism (Halmagyi and Gresty, 1979). Defective suppression of the VOR is typically associated with impaired smooth pursuit (Dichgans *et al.*, 1978; Sharpe *et al.*, 1981), suggesting that the pursuit system suppresses the VOR while objects are tracked with the head. We found an actual increase in VOR gain during attempted visual suppression above gains in darkness; this inappropriate elevation of VOR gain cannot be explained by impaired smooth pursuit. Visuospatial defects are reported to occur in parkinsonian patients who are not demented (Villardita *et al.*, 1982). Defective visual enhancement and suppression of the VOR might be a manifestation of abnormal spatial orientation or vigilance, undetected by clinical or psychometric examinations of our patients. Nonetheless, the motor defects of Parkinson's disease appear adequate to explain defective visual control of this reflex, as in brainstem and cerebellar disease (Dichgans *et al.*, 1978; Sharpe *et al.*, 1981).

Voluntary Control of the Vestibulo-ocular Reflex

Mildly affected patients were able to exert voluntary (nonvisual) control over the VOR, albeit not as effectively as with visual modulation. During rotation in darkness they increased their VOR gain close to unity by imagining a stationary target. They were unable to sustain nonvisual suppression by imagining a target moving with them. No patient with advanced disease could exert normal voluntary control over the VOR. In darkness, they neither augmented their VOR gain to normal levels, nor did they suppress it. On the contrary, during attempted voluntary suppression, there was an inappropriate increase in VOR gain above values in darkness without an imaginary target.

Voluntary suppression of the VOR, in darkness, occurs in the absence of the visual stimulus to pursuit, parafoveal image slip. In the monkey, second order vestibular neurons which are activated during both smooth pursuit and vestibular eye movements are not inhibited during visual suppression of vestibular eye movements (Tomlinson and Robinson, 1981). These observations suggest that suppression of the VOR can be independent of smooth pursuit. The defective voluntary enhancement and suppression of the VOR in darkness in Parkinson's disease was independent of visual pursuit.

The inappropriate increase of VOR gain during attempted visual and voluntary suppression was a feature of advanced disease. Subnormal cognitive function or spatial disorientation of the target position might cause disordered voluntary vestibulo-ocular responses, but such defects were not otherwise evident in these patients. Inappropriate skeletal motor reflex responses in Parkinson's disease are exemplified by exaggerated shortening responses to limb displacement (Andrews *et al.*, 1972). This is attributed to disordered long-loop cerebral cortical regulation of the spinal reflex arc (Tatton *et al.*, 1979). Similar disordered motor regulation of the VOR may be responsible for the increase in VOR gain during attempted suppression.

The low VOR gain recorded in darkness (condition 1) in advanced disease indicated functional impairment of the VOR. The near normal visual enhancement of the VOR during fixation of a stationary target, and the abnormal elevation of VOR gain during attempted visual and voluntary suppression of the reflex indicated structural integrity of brainstem smooth eye movement pathways. Human subjects with defective labyrinthine function can activate compensatory smooth eye movements during active head movements in the absence of a VOR. The compensation is achieved by the cervico-ocular reflex and by preprogrammed, nonvestibular smooth eye movements (Barnes, 1979; Kasai and Zee, 1978). Whole body oscillation eliminated the cervical-ocular reflex in our patients, but the predictable passive rotation might have permitted preprogrammed smooth eye movements to contribute to the paradoxical rise in gain. If so, such nonvestibular smooth eye movements would be inappropriately activated during attempted suppression of the reflex.

During all protocols in darkness, advanced patients had vestibular eye movements, punctuated by random periods of wandering movements, unrelated to head motion. The wandering eye movements were similar to the smooth eye movements recorded during vestibular stimulation of normal sleeping subjects (Melvill Jones and Sugie, 1972). The VOR is enhanced by alertness (Collins, 1963) and abolished during deep sleep (Melvill Jones and Sugie, 1972). Such wandering eye movements are recorded only in deep sleep. All patients in this study maintained alertness, apparently like normal subjects.

The anatomical pathways for cerebral hemisphere control of the VOR are incompletely defined. Büttner and Buettner (1978) recorded both vestibular signals of head velocity, and visual signals of retinal image velocity, in parietal neurons of monkeys. VOR imbalance after extensive unilateral cerebral lesions in monkeys and humans (Pasik *et al.*, 1960; Sharpe and Lo, 1981) indicates a functional role for such cortical relays.

No neuronal responses to vestibular stimuli have been recorded within the basal ganglia. Direct projections transmit head velocity signals from the vestibular nuclei to thalamic nuclei distinct from those which receive an input from the basal ganglia (Lang *et al.*, 1979). Thalamic vestibular areas project to cerebral cortex (Büttner and Lang, 1979) and might thus influence the corpus striatum. Defective supranuclear control of the VOR demonstrated by this study may be caused by unrecognized dysfunction within the brainstem, or by the recognized pathology of the basal ganglia.

A hierarchical organization of the basal ganglia has been proposed to control skeletal motor functions. The major outputs are from the internal globus pallidus to the thalamus and pedunculopontine nucleus, and from the substantia nigra pars reticulata to the thalamus and superior colliculus (Nauta, 1979). These projections may comprise an interface between the corpus striatum and brainstem vestibular pathways. Skeletal motor deficits in Parkinson's disease have been attributed to abnormal gain in long-loop reflexes which traverse the cerebral cortex (Tatton *et al.*, 1979). A cerebral cortical loop has been proposed to control the VOR (Sharpe, 1982). We suggest an analogous disordered hierarchical organization of VOR control in Parkinson's disease. The low VOR gains in advanced disease and the defective visual and voluntary control in all stages of disease may be secondary to an abnormality within long-loop vestibulo-ocular pathways through the cerebral hemispheres (Sharpe, 1982).

These VOR abnormalities cannot be attributed to dopaminergic or anticholinergic medications (Table 1); the defects were present with or without medication. No cholinergic or dopaminergic neurotransmission has been established within brainstem VOR pathways. We did not assess the effects of drugs longitudinally. The severity of defective VOR control paralleled the severity of somatic motor deficits. The previously unrecognized hypoactivity of horizontal ocular reflexes to passive head motion is undetected clinically by oculocephalic manoeuvres under lighted conditions, because visual enhancement of the VOR produces gains near unity. Impaired visual suppression of the reflex occurs uniformly in mild and advanced disease. Low VOR gain in darkness, impaired voluntary enhancement of VOR gain, and inappropriate elevation of gain during attempted visual suppression are all characteristic of advanced parkinsonism. These vestibular defects provide distinctive parameters of disordered motor control in Parkinson's disease.

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OCULAR MOTOR DEFICITS IN PARKINSON'S DISEASE

II. CONTROL OF THE SACCADIC AND SMOOTH PURSUIT SYSTEMS

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SUMMARY

We quantified the horizontal pursuit and saccadic function of 14 parkinsonian patients and 10 normal subjects matched for age. Eight patients had mild, and 6 advanced disease. Ocular motor deficits were more marked in patients with advanced disease. Saccadic reaction times and postsaccadic refractory periods were prolonged. Peak saccadic velocities were significantly reduced. Slow saccades may be caused by inappropriate coactivation of opposing ocular muscles. Multiple step, hypometric saccades were abnormally frequent. Correct final eye position towards a brief target flash was attained without visual feedback. Brief corrective intervals occurred after hypometric saccades. They are attributed to internal (nonvisual) efference copy feedback of eye position errors. Frequent square wave jerks were also a feature of Parkinson's disease.

Smooth pursuit gain was lowered in all patients while tracking sinusoidal targets at frequencies from 0.25 to 1 Hz. Pursuit gain was uniformly reduced at all target velocities at each frequency. This decrease in gain indicates that dysfunction of the gain element, rather than abnormal drop acceleration saturation is responsible for impaired smooth pursuit.

The results indicate that Parkinson's disease damages structures involved in the regulation of the saccadic and pursuit systems. We infer that nigrostriatal pathways, known to be damaged in Parkinson's disease, control the latency, velocity and amplitude of saccades, and the gain element of smooth pursuit.

INTRODUCTION

Parkinson's disease is a syndrome of disordered motor performance attributed to abnormal dopaminergic systems in the basal ganglia. Studies of limb motor function have demonstrated prolonged latencies and bradykinesia (Evarts *et al.*, 1981), inappropriate coactivation of agonist-antagonist muscle pairs and abnormalities of stretch and shortening responses, impaired predictive capacity and abnormalities of long-loop reflexes (Evarts *et al.*, 1979). These deficits are translated into the clinical features by which we recognize parkinsonism of any aetiology: tremor, rigidity, akinesia and bradykinesia.

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Ocular motor functions lend themselves to quantification of motor performance, relative to limb movement, because of the accessibility of eye movements for recording and the ease with which single movements can be accurately repeated. The balanced agonist-antagonist muscle pairings, low inertia of the globe and the relatively constant viscoëlastic properties of the orbit permit analysis of neural control mechanisms. Despite these attributes, few studies have quantified the function of the saccadic or smooth pursuit systems in parkinsonism. In a qualitative oculographic study Corin *et al.* (1972) observed 'cog-wheel' pursuit, hypometric saccades, gaze impersistence, subnormal optokinetic reflexes, impaired vergence and defective vertical eye movements. Shibasaki *et al.* (1979) and Teräväinen and Calne (1980) recorded an increased frequency of saccades during pursuit but they did not measure smooth pursuit. Shibasaki *et al.* (1979) described reduced saccadic velocities but did not correlate velocity with amplitude. Quantitative study of saccades has found increased latency of self-placed refixations and hypometric saccades (DeJong and Melvill Jones, 1971; Melvill Jones and DeJong, 1971; Teräväinen and Calne, 1980). The relationship between saccadic velocity and amplitude was reported to be normal.

We report a quantitative study of the saccadic and pursuit systems. We examined horizontal saccadic latency, accuracy and velocity to predictable and unpredictable target motion. Smooth pursuit gain, the ratio of smooth eye movement velocity to target velocity, was measured during horizontal tracking of sinusoidal and constant velocity targets.

METHODS AND SUBJECTS

Descriptions of the subjects and equipment used were detailed in the companion paper (White *et al.*, 1983). Briefly, we examined 14 parkinsonian patients and 10 control subjects matched for age and sex. Eye movements were recorded by photoelectric infrared oculography and data were stored on magnetic tape. After data were digitized off-line at 200 samples/s for computer analysis, the full system bandwidth was 0 to 100 Hz. Calibrations were performed before and after each paradigm. Subjects were seated with the head stabilized by chin, frontal, parietal and occipital supports.

Saccadic System

Targets for saccadic eye movements were light-emitting diodes (LED) arrayed on a stimulus arc, radius 114 cm, with the subject seated at the origin in order to eliminate changes in vergence (Sharpe *et al.*, 1979). Target position was controlled by a microprocessor. All paradigms were performed in darkness. Frequent verbal encouragement ensured alertness while saccades were made under each of four conditions. (1) *Predictable target steps.* The target was stepped from 10 deg left to 10 deg right at predictable intervals greater than 2 s. All saccadic responses to at least 50 target steps were analysed in each subject. (2) *Unpredictable amplitude target steps.* The target was stepped 5, 10, 15, 20 or 40 deg left or right at predictable intervals (3 s), in pseudorandom directions and amplitudes. Large target steps always crossed the centre so that angular displacement never exceeded 20 deg from midposition, the limits of the linear range of the infrared system. Saccadic responses to target steps (n > 150) were quantified for each subject. (3) *Unpredictable amplitude target flash.* The target was stepped in unpredictable directions and amplitudes as in condition 2, except that when the original target was extinguished, the new target was illuminated for only 40 ms and then extinguished for 2 s (fig. 1E). The LED was then reilluminated and became the fixation target. Since normal saccadic latency is approximately 200 ms, the brief target flash ensured that subjects made saccades without visual feedback. As in condition 2, saccadic data from at least 150 target steps were analysed for each subject.

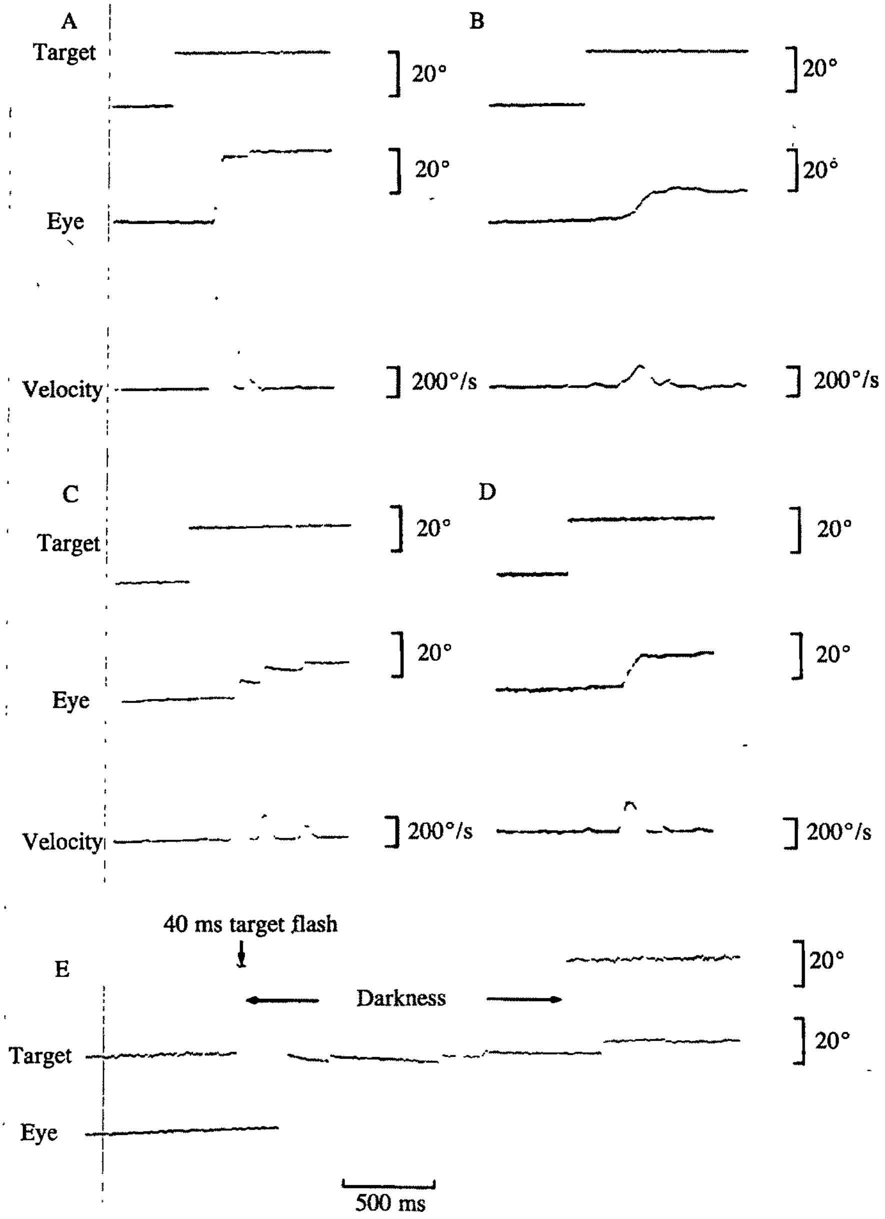


FIG. 1. Examples of digitized saccadic eye movements in response to stepped targets. A, normal subject B, patient: note slow onset and reduced peak velocity. C, patient. multiple, hypometric saccades. D, patient· slow saccade. E, patient· response to flashed target.

(4) *Unpredictable time target steps.* The target stepped from 10 deg left to 10 deg right at pseudorandom intervals ranging from 300 to 2000 ms. This paradigm made the time of target shift unpredictable, but amplitude and direction remained predictable. We recorded for 4 min in each subject. Fixation time was designated as the period from the instant of fixation of the target until the target stepped again. Fixation time was measured to differentiate between prolonged latencies to target steps and a prolonged refractory period after refixation, before another saccade could be generated. Refractory delay and initiation delay could both be construed as saccadic akinesia, but quite separate mechanisms may be responsible.

Fixation stability was observed in all patients and quantified in 8 patients while fixating a stationary LED target for 3 min. The frequency of square wave jerks was recorded.

Smooth Pursuit System

Subjects were instructed to follow a laser target (0.25 deg at the retina) projected from the rear on to a screen 170 cm from their nasion. Target movement was achieved by reflecting the laser beam on to a galvanometer mounted mirror and was controlled by a microprocessor. Target motion was 20 deg peak-to-peak. Ambient lighting was maintained at a low level.

1. *Predictable ramps.* The target moved in predictable directions and velocities. Fixed intervals between each ramp also made timing predictable. Ramp velocities were 10, 20 and 40 deg/s. We analysed responses to 80 ramps at each velocity for each subject.

2. *Predictable sinusoids.* The target moved sinusoidally at constant frequencies of 0.25, 0.5 or 1.0 Hz. Peak-to-peak amplitude was 20 deg. Peak velocity was 16, 31 and 63 deg/s, yielding peak target accelerations of 25, 99 and 395 deg/s/s, respectively. The sinusoidal motion elicited a large range of target velocities with low acceleration demands relative to ramp targets. We analysed all responses to 25 target cycles at each frequency for each subject.

Data Analysis

Digitized eye position data were displayed on a graphics terminal simultaneously with a differentiated velocity trace. For target steps, cursors placed on the target channel defined the time, direction and amplitude of target motion. Cursors on the eye position channel delineated the onset and termination of each saccade. The peak velocity was measured from the eye position trace between 2 cursors, 10 ms apart, at the segment corresponding to the peak of the differentiated signal.

For pursuit paradigms, the target movement was marked and the cursors were placed on the eye position channel at the onset and completion of all smooth eye movement segments. A computer program divided sinusoidal target motion into segments of approximately uniform velocity, and selected time-locked smooth eye movement segments; pursuit gain was then computed for a range of velocities at each target frequency.

Statistical analyses of all data were performed using the nonparametric Mann-Whitney U test.

RESULTS

Patients were divided into two groups, mild and advanced, on the basis of severity of rigidity and bradykinesia, and the duration of disease, as described in the companion article (White *et al.*, 1983).

Saccadic System

1. *Predictable target steps and 2, unpredictable amplitude target steps.* Protocols 1 and 2, in which target timing was always predictable, are considered together since

latencies and saccade metrics did not differ significantly for any individual subject between the two conditions. Normal subjects and patients often made eye movements before target steps, whether or not the amplitude and direction of target step were predictable. These anticipatory movements towards the expected goal were of two types: either saccades, or smooth eye movements which had velocities less than 1 deg/s. When the direction and amplitude of target step were unpredictable (condition 2), subjects frequently made errors in the direction of their anticipatory movements but persisted in attempts to predict. Anticipatory movements, having negative latencies, were excluded from latency data. Patients with advanced disease had significantly longer mean saccadic latencies than normals ($P < 0.001$; Table 1; fig. 2A). There was a wide intrasubject range of saccadic latencies even for mildly affected patients (SD ± 80 ms) compared to normal subjects (SD ± 40 ms).

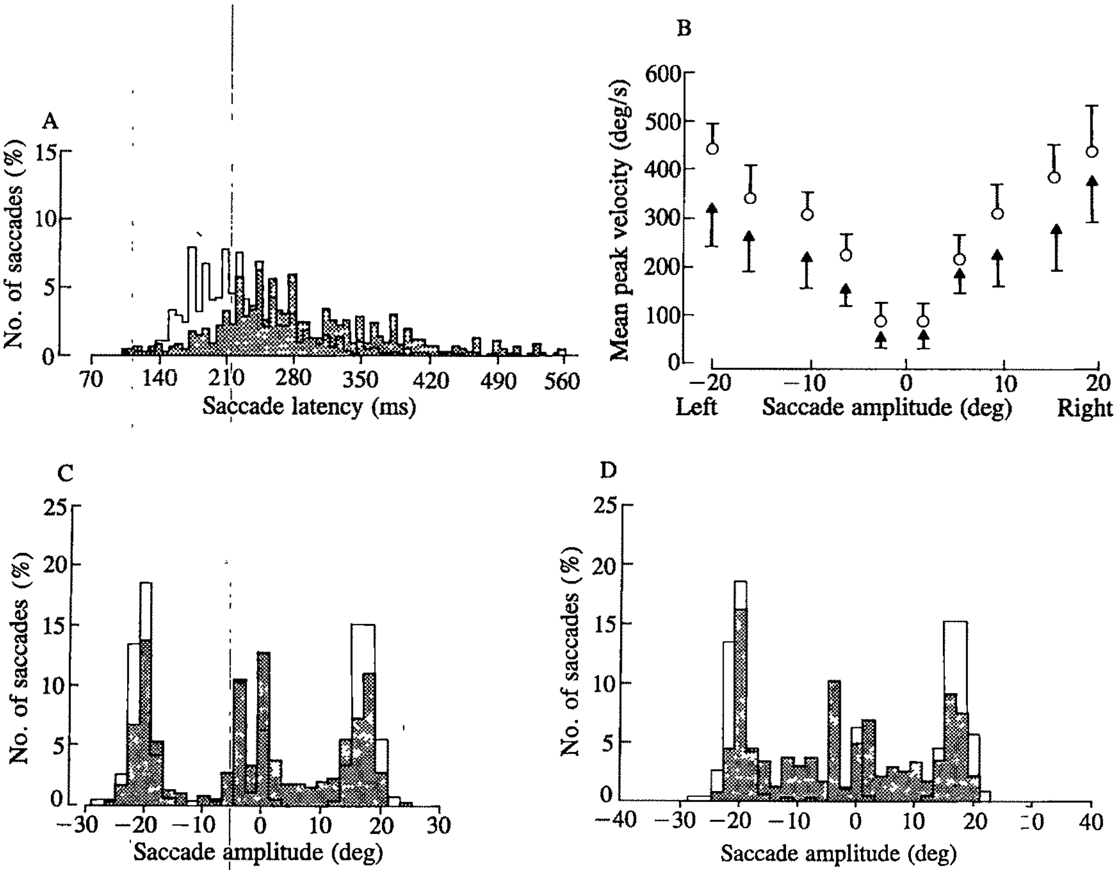


FIG. 2. A, histogram of saccade latencies for patients with advanced disease (crosshatched columns) and normal subjects (open columns). B, graph of saccade mean peak velocity *vs* amplitude for advanced patients (▲) and normal subjects (○). Error bars indicate 1 SD. C, histogram of frequency of saccades of varying amplitudes in response to predictably timed target steps of 20 deg; mild patients (crosshatched columns); normal subjects (open columns). D, histogram of saccadic amplitude for patients having advanced disease (crosshatched columns) shows more frequent saccadic hypometria. Negative amplitude indicates leftward saccades, positive rightward.

The peak velocity-amplitude relationship of 4, 10 and 18 deg saccades, made by patients and normals, were compared. We obtained these velocities from conditions 1 and 2, using over 15 saccades at each amplitude for each subject (Table 1). Patients demonstrated far more variability than normals. Mean saccadic velocities were significantly slowed at all amplitudes for advanced patients ($P < 0.01$; Table 1; fig. 2B), but velocities were within the normal range (normal mean ± 2 SD). Patients also generated many more saccades terminated by slow glissadic movements than did normal subjects. In patients, initial responses, after target steps, were frequently slow movements, continuous with the saccade, which were not by their timing anticipatory (fig. 1B). Such slow acceleration was not a feature of saccades in normal subjects.

TABLE 1. SACCADIC LATENCIES AND VELOCITIES FOR PREDICTABLY TIMED TARGET STEPS

		Patients	
	Normals	*Mild*	*Advanced*
Latency (ms)	220±40	270±80	360±90**
	Mean peak velocity (deg/s)		
Saccade amplitude			
4 deg	176±15	157±36*	130±34***
10 deg	314±43	288±49***	246±56**
18 deg	396±54	387±66	296±55***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Saccadic inaccuracy was frequent in patients. They made multiple hypometric steps to refixate the target (fig. 1C). Hypometria was measured by computer histogram plots of the frequency of saccades of all amplitudes in response to a target step of constant amplitude (fig. 2C, D). Normal subjects made primary saccades close to or equal to the amplitude of the target step of 20 deg. Patients made initial hypometric saccades unrelated in amplitude to the size of the target step. They were followed by a corrective saccade, beginning at a mean interval of 150 ms (range 10 to 1000 ms) after the completion of the primary saccade (fig. 1C). Mean correction time was not significantly different from normal subjects but the range was greater. Hypometric saccadic segments had the same reduced peak velocity-amplitude relationship as the patients' normometric saccades.

3. *Unpredictable amplitude target flash.* This paradigm examined saccadic accuracy without visual feedback. Nine patients, 4 with advanced disease and 3 normal subjects, were examined. Accuracy of saccades to a flashed target did not differ from accuracy to a continuous target in patients or normals. Patients generated multiple hypometric saccades but attained the position of the target flash prior to its reillumination like normal subjects (fig. 1E). Latencies, saccadic velocities

and corrective times were comparable to those obtained with constantly lighted targets.

4. *Unpredictable time target steps.* Variation of the timing of target steps prolonged the latency for saccades (*see* Tables 1 and 2). Fixation times were grouped in bins and correlated with latency (Table 2). Normal subjects demonstrated only mild lengthening of latency for refixations performed after periods of fixation less than 300 ms. Although mildly affected patients had prolonged latencies, these did not differ significantly from normal. Advanced patients showed significantly prolonged latencies (Table 2). After brief fixation periods the increase in saccadic delay was twice that of normal subjects. In other words, the time required to initiate a saccade increased as the time available for target sampling (fixation time) decreased.

TABLE 2. SACCADIC LATENCY *VS* DURATION OF TARGET FIXATION TIME FOR UNPREDICTABLY TIMED TARGET STEPS

		Fixation time (ms)					
Subjects		*< 200*	*< 300*	*< 400*	*< 500*	*< 800*	*> 800*
Normals	LATENCY	390	370	320	270	240	210
Mild patients		440	340	350	250	220	210
Advanced patients		670*	630*	400*	380	330**	260*

* $P < 0.05$, ** $P < 0.01$. Latencies are the mean of the mean values for each subject.

Square wave jerks, consisting of horizontal saccades followed after an interval by saccadic return to the fixation position, occurred far more frequently in patients with Parkinson's disease (mean frequency 52/min ± 29, range 5–82) than in normal subjects (Herishanu and Sharpe, 1981). Abnormally frequent square wave jerks were observed both during fixation and low velocity pursuit.

Smooth Pursuit System

1. *Predictable ramps.* All but one patient (Case 14, White *et al.*, 1983) showed significant reduction in smooth eye velocities while pursuing ramps at both 10 and 20 deg/s (Table 3). Neither patients nor normals pursued the repeated single ramps successfully at 40 deg/s. Patients, like normals, generated anticipatory smooth eye movements before target movement (fig. 3). These anticipatory movements frequently attained velocities up to 10 deg/s. Saccadic intrusions, in both directions, were frequent, but patients with advanced disease adopted a stratagem of saccadic pursuit, even at the lowest target velocities (fig. 3). This smooth pursuit eye movement deficit is illustrated by histograms of cumulative time spent in smooth

TABLE 3. SMOOTH PURSUIT OF PREDICTABLE SINGLE RAMPS

	Mean eye velocity (deg/s)		
		Patients	
Target velocity	*Normals*	*Mild*	*Advanced*
10 deg/s	8.99±0.72	8.49±0.59*	7.29±1.97*
20 deg/s	15.82±2.02	13.22±1.89***	10.33±3.49***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

pursuit expressed as a percentage of the total time that the target moved across the screen at each velocity (fig. 4). Patients demonstrated greater variability and spent more time at lower pursuit gain than normals, a deficit more evident in advanced disease (fig. 4; Table 3).

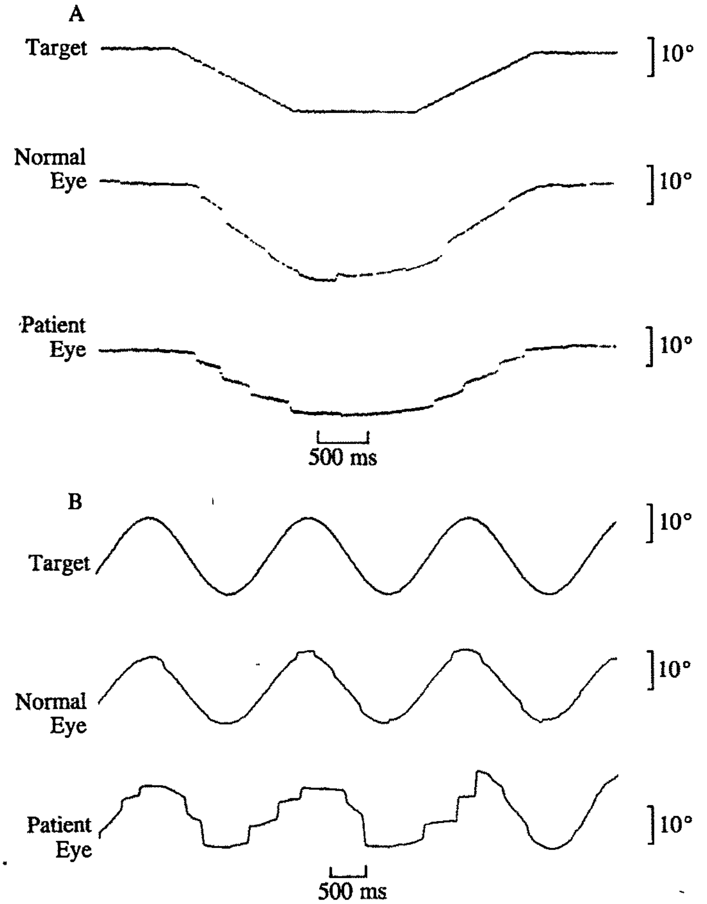


FIG. 3. Examples of digitized smooth pursuit movements made by patients with advanced disease and normal subjects. A, single repeated ramps. B, sinusoidal target. Right is upward, left downward.

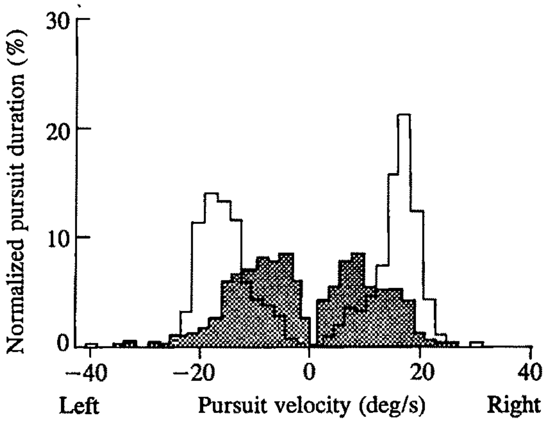


FIG. 4. Histogram of normalized pursuit duration (cumulative duration of smooth pursuit eye movements expressed as a percentage of cumulative ramp duration) for advanced patients (cross-hatched columns) and normal subjects (open columns), while tracking 20 deg/s ramps.

2. *Predictable sinusoids.* Normal subjects pursued targets at 0.25 and 0.5 Hz with gain close to unity; at 1.0 Hz, gain declined to 0.55 (Table 4; fig. 5). Pursuit gain, the ratio of smooth eye movement velocity to target velocity, was independent of target velocity at each target frequency (for example, 0 to 63 deg/s at 1.0 Hz; fig. 6). The relationship between target velocity and smooth eye movement velocity indicated that pursuit gain decreased with increasing target frequency not with increasing target velocity. Patients had significantly lower pursuit gains at each frequency than controls (Table 4; fig. 5). All but Case 14 substituted saccadic tracking for defective smooth pursuit at even the lowest frequency.

Smooth pursuit depends on visual feedback; it is a closed-loop negative feedback system (fig. 7). Closed-loop pursuit gain was measured as the ratio of eye velocity to target velocity for each target segment, then averaged to obtain mean pursuit gains for each target frequency over the range of target velocities. We estimated pursuit

TABLE 4 SMOOTH PURSUIT OF SINUSOIDAL TARGETS

	Closed-loop pursuit gain		
		Patients	
Frequency (Hz)	*Normals*	*Mild*	*Advanced*
0.25	0.92±0.07	0.84±0.09*	0.70±0.14**
0.5	0.90±0.10	0.74±0.12**	0.54±0.23***
1.0	0.55±0.12	0.49±0.12	0.35±0.13*
		Open-loop pursuit gain	
0.25	11.5	5.25	2.33
0.5	9.0	2.8	1.2
1.0	1.2	0.95	0.54

No significance was obtained at 1.0 Hz for mildly impaired patients but 2 patients from this group and 3 more severely impaired patients were unable to follow at this frequency. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

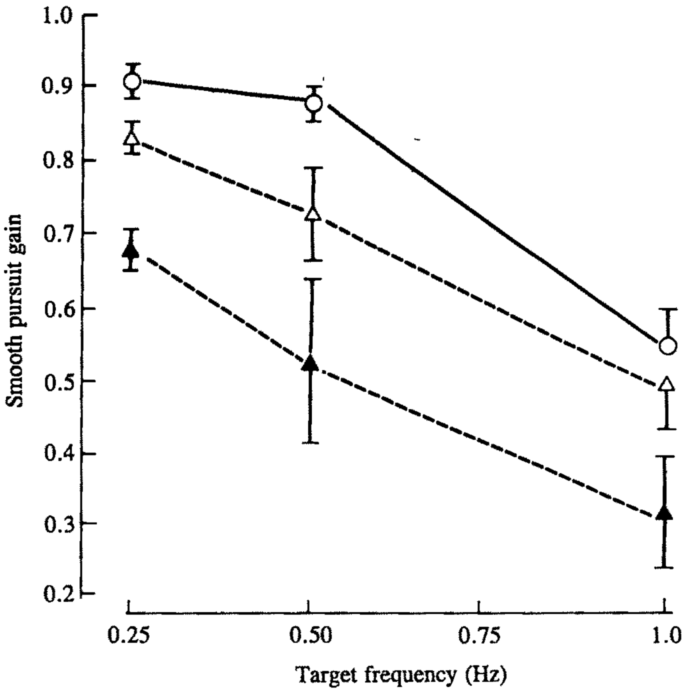


FIG 5. Graph of smooth pursuit gain *vs* target frequency for sinusoidal targets. Patients with advanced disease (▲) Patients with mild disease (△). Normal subjects (○). Error bars indicate ±1 SD.

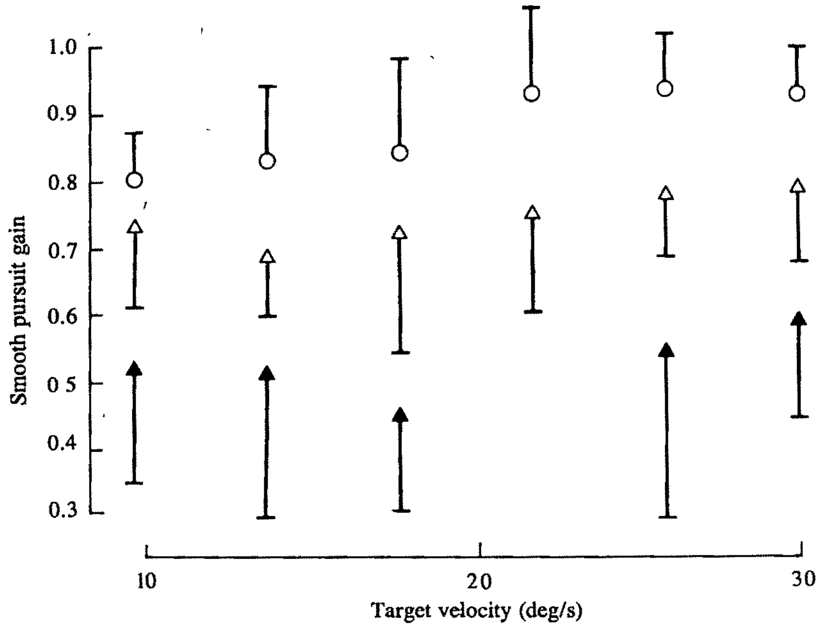
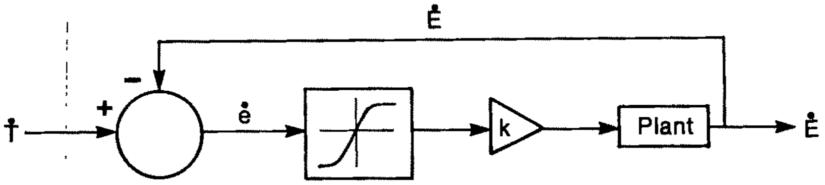


FIG. 6. Graph of smooth pursuit gain *vs* target velocity for a sinusoidal target at 0.5 Hz. Patients with advanced disease (▲). Patients with mild disease (△). Normal subjects (○).

system performance by calculating the open-loop gain (k) from the closed-loop gain (G) where k = G/1-G. Although closed-loop gain was decreased by less than 30 per cent for target velocities under 30 deg/s (at 0.25 and 0.5 Hz in the sinusoidal protocols), calculated open-loop gain was decreased by about 70 per cent (Table 4).



$$G = \dot{E}/\dot{T} = \frac{k}{1 + k}$$

FIG. 7. Simplified model of smooth pursuit system. Proceeding from the left, eye velocity ($\dot{E}$) is subtracted from target velocity ($\dot{T}$) to yield retinal slip velocity ($\dot{e}$). This signal is passed through a saturating nonlinearity, depicted by the box containing a sigmoid curve, and then multiplied by a gain factor, k, before being fed to the orbital plant (eye muscles and orbital mechanical properties) resulting in an eye velocity ($\dot{E}$) which is the output of the system. The negative feedback loop causes the overall system gain (G) to be k/1+k.

DISCUSSION

This study documents abnormalities of saccadic initiation and trajectory, and smooth pursuit gain, not previously quantified in Parkinson's disease. We examined patients taking L-DOPA and anticholinergic medications, in combination or alone, as well as untreated patients. Ocular motor dysfunction occurred regardless of medication. We did not study the effects of medications longitudinally. Highstein *et al.* (1969) recorded improvement in saccadic speed and accuracy after L-DOPA in 2 patients. In our 14 patients the severity of ocular motor impairment correlated with the duration of the disease and the severity of bradykinesia and rigidity.

Saccadic System

Saccadic delay. The mean latency of saccades to target steps was markedly increased in advanced disease (Table 1). Both patients and normal subjects frequently initiated saccades at short latency when target timing was predictable (fig. 2A). Patients, like normal subjects, made anticipatory movements before the target moved. Most were saccades, but a few were smooth eye movements that did not exceed 1 deg/s. Both our patients and normals generated anticipatory smooth eye movements at velocities up to 10 deg/s before ramp targets. Short latency saccades and anticipatory eye movements to regular target motion signified preserved ocular motor prediction in parkinsonism. This relative integrity of ocular motor prediction contrasts with impairment of anticipatory limb movements (Flowers and Downing, 1978).

The prolonged reaction time for limb movement (akinesia) is disproportionately increased for visually triggered responses when compared with kinaesthetic responses (Evarts *et al.*, 1981). In our patients, saccadic delay to unpredictably timed targets was disproportionately increased after brief periods of target fixation (Table 2). The large increment in patients' reaction time (approximately 340 ms) compared with that of normals (approximately 150 ms), greatly exceeds the increase in delay of visual evoked potentials in Parkinson's disease (approximately 15 ms) (Bodis-Wollner and Yahr, 1978). This saccadic akinesia cannot be explained by visual afferent delay alone. Since saccadic delay after prolonged fixation was relatively brief (330 ms), the increment in delay after brief fixation (latency 670 ms) cannot be explained by absolute delay in motor efferent pathways.

Normal saccadic responses to visual stimuli usually occur at discrete intervals of approximately 200 ms. A sampled-data system model was proposed to explain this behaviour (Young and Stark, 1962). However, observation of shorter latency responses and visual modification of saccades in flight prompts revision of the sampled-data concept (Hallett and Lightstone, 1976). Robinson (1973) proposed parallel processing for saccades of specific amplitude and direction. According to this hypothesis, each parallel process can initiate a saccade and cancel others. In our patients, saccadic delay increased as sampling time decreased (fixation time; Table 2). The increased time required for sampling could indicate increased refractoriness in sampled-data behaviour. This refractory delay implies that defective selection of channels that trigger saccades might be responsible for saccadic akinesia in Parkinson's disease. This explanation is highly speculative, and other mechanisms might account for refractory delay.

Dementia and cerebral cortical damage also cause prolonged saccadic latency (Pirozzolo and Hansch, 1981; Sharpe *et al.*, 1979). Dementia occurs more frequently in Parkinson's disease than in an age-matched population (Lieberman *et al.*, 1979) and cerebral cortical degeneration can occur without dementia in Parkinson's disease (Boller *et al.*, 1980). Our patients who had advanced motor deficits and normal intellectual function (White *et al.*, 1983) had saccadic delay. The delay may be an otherwise undetected disorder of vigilance that results from cerebral cortical or basal ganglia dysfunction in Parkinson's disease.

Frequent square wave jerks signified fixational instability. Although prominent in cerebellar system disease, they are also common in patients with focal cerebral hemisphere damage (Sharpe *et al.*, 1982). Our recordings indicated that square wave jerks are a feature of Parkinson's disease.

Slow saccades. Peak velocities for saccades of defined amplitudes, although within the normal range, were significantly reduced and more variable in patients (fig. 2B; Table 1). Slowing was more marked in patients with advanced disease (Table 1). Saccades are probably initiated by supranuclear trigger signals that inhibit pause cells in the midline pontine tegmentum (Robinson, 1975). Pause cells, in turn, are thought to inhibit presaccadic burst units in the pons. In the monkey, van Gisbergen *et al.* (1981) recorded from motor neurons in the abducens nuclei, and from medium-lead burst neurons in the pontomedullary reticular formation, which discharge before saccades. Burst cells fire for saccades in all directions. Motor neurons discharge for saccades in both horizontal directions but their firing sequence varies with the direction of saccades, thereby defining on and off directions. The on-direction burst drives the saccade, and subsequent off-direction firing of burst cells on the opposite side of the pons may be responsible for dynamic braking of the eye at the end of saccades.

The difference between on-direction burst rate and off-direction burst rate correlates with instantaneous eye velocity. Inhibitory burst neurons in the medullary reticular formation are thought to inhibit motor neurons reciprocally during saccades in off-directions (Hikosaka *et al.*, 1978). The reciprocal agonist-antagonist discharge of motor neurons is determined by synchronized activity of on-direction burst neurons, off-direction burst neurons and inhibitory burst neurons.

The slowed saccades recorded in our patients indicate disordered regulation of motor neuron innervation. The pontine tegmentum is the only supranuclear site where damage is proven, by pathological correlation, to cause marked slowing of saccades (Sanders, 1975). Progressive supranuclear palsy is a parkinsonian syndrome in which slow hypometric horizontal saccades accompany vertical ophthalmoplegia (Troost and Daroff, 1977). Degeneration of the pontine reticular formation (Steele *et al.*, 1964) is a feature of the disorder that can explain slowed saccades. However, the pontine reticular formation is considered to be structurally intact in idiopathic Parkinson's disease (Alvord *et al.*, 1974). The occurrence of many saccades with normal peak velocities in our patients implies a normal complement of burst cells in the pons.

Slatt *et al.* (1966) and Chaco (1971) recorded slowed development of the electromyographic (EMG) interference pattern is agonist ocular muscles, in association with inappropriate coactivation of antagonist muscles during saccades. We suggest that the slowed saccades of our patients are caused by impaired reciprocal activation of agonist on-direction burst cells, antagonist off-direction burst cells and inhibitory burst cells.

Cofiring of muscles can cause ocular retraction. For example, patients with paralysis of upward saccades from dorsal midbrain damage exhibit retraction of the eyes when they attempt to make upward saccades (Gay *et al.*, 1963). We did not observe ocular retraction during saccades in our patients. The amount of coactivation required simply to slow saccades would not be expected to cause visible retraction.

Hypometric saccades. Patients, unlike normal subjects, frequently require multiple saccadic steps to attain desired eye position. Inappropriate coactivation of agonist and antagonist ocular muscle pairs may explain slow saccades but not hypometric saccades. After a brief (40 ms) target flash, patients achieve final desired eye position in complete darkness, without the benefit of continuous visual feedback, indicating that desired eye position is correctly coded by the retinal error in Parkinson's disease. Robinson (1975) proposed a model in which desired eye position signals the duration of burst cell discharge while a trigger signal inhibits the pause cells, thus releasing the burst cell discharge. According to this hypothesis, collaterals of burst cells maintain inhibition of the pause cell and an internal copy of eye position signal (efference copy) is fed back to inhibit the burst cell. When the efference copy of eye position is equal to desired eye position, burst cells cease firing, pause cells resume activity and the saccade stops.

Stimulation of pause cells in the medial pontine reticular formation of monkeys stops saccades while in progress, and if the stimulus is sufficiently brief, saccades subsequently resume their course to near correct final eye position (Keller, 1977). The hypometric saccades of parkinsonism could be explained by inappropriate pause cell activation while a saccade is in progress. Pause cell activity might explain the irregular development of the EMG interference pattern in agonist ocular muscles (Slatt *et al.*, 1966; Chaco, 1971), thereby causing the slow saccadic acceleration recorded in our patients.

Following an initial hypometric step, further saccades were generated at intervals ranging from 10 to 1000 ms. These corrective saccades might be preprogrammed, but a strategy of multiple saccades would delay refoveation. After pathologically hypometric steps, corrective saccades could be mediated by visual feedback, orbital proprioceptive feedback or by an internal (nonretinal) efference copy of eye position. The occurrence of corrective saccades in the target flash condition indicated that visual feedback was not required to generate corrective saccades. Known latencies of orbital proprioceptive responses *via* the cerebellum or superior colliculi, proposed relays for orbital proprioception, are too long to explain corrective intervals less than about 30 ms (Kimura and Maekawa, 1981; Ron and Robinson, 1973; Rose and Abrahams, 1978; Wurtz and Albano, 1980). Corrective saccades after shorter intervals must be determined by mismatch of desired eye position with an internal efference copy of eye position. The short latency corrective saccades indicate that pathways transmitting internal feedback of eye position are intact in Parkinson's disease.

Smooth Pursuit System

Smooth pursuit gain, the ratio of eye velocity to target velocity, is lowered in Parkinson's disease. By holding target acceleration constant while changing target velocity, amplitude and frequency, Lisberger *et al.* (1981) demonstrated that normal pursuit system gain is insensitive to changes in target velocity or frequency. Then while holding target velocity constant by changing target amplitude and frequency inversely, they showed that pursuit gain decreases at high target accelerations. This acceleration limitation on normal pursuit gain is called a saturating nonlinearity in engineering terms; it is depicted by the box containing a sigmoid curve in fig. 7.

One of the advantages of negative feedback systems such as smooth pursuit (fig. 7) is that the closed-loop gain ($k/1+k$) is relatively insensitive to changes in open-loop gain (k). However, the open-loop gain is determined by neural circuits; it is the pursuit parameter that assesses neurological dysfunction. Direct measures of open-loop gain require artificial stabilization of a retinal image (Pola and Wyatt, 1981) or monocular ophthalmoplegia. We calculated open-loop gain from the measured closed-loop gain (G). At frequencies of 0.25 and 0.5 Hz, gain was reduced uniformly at all target velocities, whether target acceleration was large or small. Changes in the saturating nonlinear element that limits acceleration would reduce eye acceleration and thereby reduce the frequency at which saturation (gain decrease) occurred. However, changes in the saturating nonlinear element would not affect the low frequency performance where target acceleration is minimal. The uniform reduction in gain at low frequencies (fig. 5) indicates that the pursuit defect in Parkinson's disease is a disorder of the gain element, not the saturating nonlinearity alone.

Reduction in pursuit gain at all target frequencies in Parkinson's disease is similar to that recorded in cerebellar system degeneration in man (Zee *et al.*, 1976), and after flocculectomy in monkeys (Zee *et al.*, 1981). It differs from impaired pursuit after cerebral cortical damage, when low frequency pursuit gain approaches unity but decreases (saturates) as frequency increases (Sharpe *et al.*, 1979). The difference in the pursuit performance suggests that cerebral cortical lesions damage the nonlinear saturating element of the pursuit loop, whereas Parkinson's disease, like cerebellar degeneration, involves the gain element. Little is known about the anatomical substrates for smooth pursuit. We infer that dopaminergic nigrostriatal pathways affect the gain element of the pursuit system.

Several sites of potential dysfunction could disrupt saccadic performance. Schiller *et al.* (1980) demonstrated that combined lesions of frontal eye fields and superior colliculus produce slowed small saccades. The frontal eye fields project to the corpus striatum (Künzle and Akert, 1977), which in turn has a major outflow *via* the substantia nigra pars reticulata to the superior colliculus (Nauta, 1979). Wurtz and Hikosaka (1981) recorded from cells in the substantia nigra pars reticulata which modulate with saccades and project to the superior colliculus. Microstimulation in the superior colliculus activates pause cells in the pontine reticular formation (Raybourn and Keller, 1977) and elicits retinotopically coded saccades (Stryker and Schiller, 1975). Lesions of the superior colliculus produce delayed, slowed and hypometric saccades (Schiller *et al.*, 1980) similar to those in Parkinson's disease. We suggest that involvement of this nigrocolliculoreticular circuit may explain the saccadic deficits that we have described in Parkinson's disease.

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MICRONEUROGRAPHIC EVIDENCE OF EXCESSIVE SYMPATHETIC OUTFLOW IN THE GUILLAIN-BARRÉ SYNDROME

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SUMMARY

We investigated 3 patients with moderate to severe Guillain-Barré syndrome (GBS) who had transient hypertension and tachycardia during the illness. Microelectrode recordings of muscle nerve sympathetic activity were made in the peroneal nerve once during the acute phase when hypertension and tachycardia were present and twice after recovery from these symptoms. During the acute recording the level of sympathetic activity was considerably higher than after recovery, when the two recordings showed reproducible levels. The normal cardiac rhythmicity was preserved except during brief periods in one patient. Control recordings were made during the acute phase and after recovery in 4 GBS patients without clinical signs of autonomic involvement and twice in 15 healthy subjects. In each control subject the level of sympathetic activity was reproducible, although recordings were made with intervals of two days to four years. The findings show that in the GBS with transient elevations of blood pressure and heart rate there is sympathetic hyperactivity. It is suggested that the increased activity is due to reduced inhibition of the vasomotor centres caused by lesions of the afferent limbs of arterial and perhaps mainly intrathoracic baroreflexes.

INTRODUCTION

Dysfunction of the autonomic nervous system may occur in the Guillain-Barré syndrome (GBS). There may be decreased sympathetic and parasympathetic function (Birchfield and Shaw, 1964; Lichtenfeld, 1971; Tuck and McLeod, 1981), but cases with transient hypertension and tachycardia are not rare (Haymaker and Kernohan, 1949; Eiben and Gersony, 1963; Davies and Dingle, 1972; Bredin, 1977) in which sympathetic hyperfunction has been suggested as an underlying mechanism (Lichtenfeld, 1971; Durocher *et al.*, 1980). Elevated levels of catecholamines (Mitchell and Meilman, 1967; Davies and Dingle, 1972; Davidson and Jellinek, 1977; Durocher *et al.*, 1980) provide some support for this view, but no direct evidence of sympathetic hyperfunction has been presented.

With a microelectrode technique sympathetic discharges can be recorded in human peripheral nerves (Hagbarth and Vallbo, 1968; Vallbo *et al.*, 1979). Such recordings have shown that the normal sympathetic vasoconstrictor outflow to muscles participates in blood pressure control and consists of bursts of impulses synchronous with the pulse, which occur predominantly during transient reductions of blood pressure (Delius *et al.*, 1972; Sundlöf and Wallin, 1978*a*). The level of activity at rest (expressed as bursts/100 heart beats or bursts/minute) varies considerably between individuals but is remarkably constant for a given individual, even with years between the recordings (Sundlöf and Wallin, 1977). This difference in amount of activity between individuals does not correlate with interindividual differences in blood pressure levels (Sundlöf and Wallin, 1978*a*).

The present paper describes findings of increased muscle sympathetic activity (MSA) in three GBS patients with transient hypertension and tachycardia.

PATIENTS AND METHODS

Recordings of multiunit MSA were performed in 3 patients with acute GBS with tachycardia and temporary hypertension. Two control groups were studied: one consisted of 4 patients (aged 31 to 61 years) with acute GBS without signs of autonomic involvement (GBS control) and the other of 15 healthy volunteers, 20 to 58 years of age. In the patients with autonomic symptoms, nerve recordings were made during the acute illness and on two occasions following recovery from autonomic symptoms. Follow-up recordings were made at 6 and 19, 6 and 34, and 5 and 8 months after the first recording in the 3 patients, respectively. The GBS control patients were examined twice, once during the acute illness and once after recovery—the second recording was made 2 months to 4 years after the first. Recordings in healthy volunteers were made twice with an interval of 2 days to 4 years.

Informed consent was received from all subjects and the study was approved by the Ethics Committee of the Medical Faculty, University of Uppsala. The recordings caused only minimal discomfort and no long lasting after-effects occurred.

Case Histories

Case 1. In October 1978 a 45-year-old man developed numbness of the limbs and slight ataxia together with weakness and areflexia. During the following three weeks progressive deterioration to flaccid quadriparesis, severe bilateral facial palsy and respiratory paralysis occurred. Assisted ventilation was needed for two weeks and then slow improvement followed, although half a year later moderate facial weakness, profound weakness of foot dorsiflexion, markedly impaired sensation and moderate limb ataxia still persisted. In May 1980 he still displayed foot weakness, impaired sensation and ataxia. Motor conduction velocities were markedly decreased during the acute illness and only slightly improved in May 1980. Maximal CSF protein content was 0.96 g/l. During the two-weeks preceding the respiratory failure, his resting heart rate was 100 to 115 beats/min and blood pressure (recorded with a cuff on the upper arm) around 150/100. When his neurological deficit started to improve blood pressure and heart rate returned to normal (120 to 140/80, heart rate 65 beats/min). The first nerve recording was performed on the fourth day of hypertension.

Case 2. In June 1979, ten days after having conjunctivitis, a previously healthy 21-year-old man experienced facial stiffness and limb paraesthesiae. External ophthalmoplegia, decreased corneal sensation, dysarthria and moderate limb weakness developed within one week. On the day of admission to hospital resting heart rate was 155 to 178 beats/min and blood pressure 165/115. During the next five days heart rate became progressively reduced from 160 to 100 beats/min and blood pressure fell to 150/105 and became normal during the following week. Meanwhile rapid improvement of the neurological deficit occurred. Recovery was complete within three months from the onset. Motor conduction velocities remained normal but F-latencies were prolonged during the acute illness. CSF protein content was maximally 1.47 g/l. After recovery blood pressure was 120/80 and heart rate 70 beats/min. The first nerve recording was made on the day after admission to hospital.

Case 3. A 23-year-old man had a sore throat in October 1981 and infectious mononucleosis was diagnosed. Ten days later he experienced limb paraesthesiae and developed moderate bilateral facial palsy. During the next ten days his condition deteriorated with development of impaired sensation, marked ataxia and moderate limb weakness. Meanwhile hypertension developed with maximal blood pressure of 180/130. Concomitantly resting tachycardia with heart rates of 130 beats/min was noted and treatment with a β-receptor antagonist was instituted. On the following two days blood pressure was 170/110 and 150/100, respectively, and thereafter normal pressures (110 to 130/70 to 75) were measured. Hypertension and tachycardia did not recur but further progression of leg weakness occurred and a high dosage prednisone treatment was given (2500 mg in five days). A slow recovery followed but in March 1982 he still had weakness of the legs, slight facial paresis and areflexia. In June 1982 recovery was almost complete. The β-blocking treatment was continued for three weeks. Motor conduction velocities were normal but distal conduction time was prolonged in motor nerves. Maximal CSF protein content was 1.87 g/l. Microneurography was performed on the second day of tachycardia and hypertension, before treatment with the β-receptor antagonist was instituted.

Recording Procedure

Tungsten microelectrodes with an uninsulated tip diameter of 1 to 5 μm were used for the *nerve recordings.* A reference electrode of similar type was inserted subcutaneously about 2 cm from the recording electrode. The signal was amplified in two steps (total gain 20 000 to 50 000 ×) and fed through a band pass filter (width 700 to 2000 Hz) and a noise discriminator to improve signal-to-noise ratio. An RC integrating network (time constant 0.1 s) was used to obtain a mean voltage display of the nerve discharges. An ECG was recorded with chest electrodes. Analogue signals of amplified, filtered and mean voltage neurograms and ECG were stored on FM tape (Sangamo Sabre VI) for subsequent analysis.

All recordings were made in the peroneal nerve at the fibular head. The electrode was inserted through intact skin in the awake unanaesthetized subject, who was either supine or sitting in a semi-recumbent position (the same position was adopted at all recordings for a given individual). The nerve was localized with the aid of electrical stimuli delivered through the electrode, evoking muscle twitches when the electrode was close to a muscle nerve fascicle. Afferent mechanoreceptor activity, evoked by stretching or tapping the appropriate muscle, provided evidence that the electrode had penetrated a muscle nerve fascicle. Then small adjustments of the electrode were made until the characteristic MSA was recognized. The activity was then recorded during 10 to 15 min rest. Evidence of the sympathetic nature of the recorded discharges was summarized by Vallbo *et al.* (1979).

Skin sympathetic effector organ function was tested by recording reduction of skin resistance (galvanic skin response) in the feet and pulse amplitudes in the big toes following an arousal stimulus or a sudden deep inspiration. Ag-AgCl electrodes and a photoelectric plethysmograph, respectively, were used for these purposes (for details *see* Fagius and Wallin, 1980*a*).

Analysis Procedure

The mean voltage neurogram and ECG were displayed on paper by an ink-jet recorder (Mingograph 800) at two different paper speeds, 5 mm/s and 25 mm/s. From the 5 mm/s display, bursts were counted and expressed as bursts/100 heart beats and bursts/min. From the 25 mm/s display, duration of bursts in the mean voltage neurogram and R-R intervals in the ECG were measured. In addition, sympathetic reflex latencies were measured from the R-wave of the ECG to the peak of corresponding burst in the mean voltage neurogram; owing to the delay from haemodynamic events and nerve conduction time, the inhibition of a burst (the peak being taken as start of inhibition) will appear approximately 1.3 s after the appropriate heart beat (Fagius and Wallin, 1980*a*). Reflex latency (which to a large extent reflects conduction velocity in postganglionic C-fibres) was calculated as the mean of 35 to 50 latencies measured from the 25 mm/s paper display.

RESULTS

The Level of Activity

During the acute phase of the disease the 3 patients with transient hypertension and tachycardia had considerably higher incidences of sympathetic bursts than after recovery. This is illustrated in figs. 1 and 3, which show segments of experimental records from the acute phase and the first follow-up recording. On the other hand in none of the patients was there a significant difference between the levels of activity in the two follow-up recordings and neither did the levels of activity differ significantly between the two recordings in 15 normal subjects and the 4 GBS control patients. Data from all GBS patients are summarized in the Table, and in fig. 2 the levels of sympathetic activity in recordings 1 and 2 are plotted against each other for all subjects. For the 3 GBS patients with transient hypertension and tachycardia, the two recordings during recovery are also included in the graphs.

Pulse Synchrony, Reflex Latency and Burst Duration

In the normal subjects and the 4 GBS control patients the sympathetic impulses were grouped in bursts which always occurred in the cardiac rhythm. This was usually also the case in the 3 GBS patients with transient hypertension and

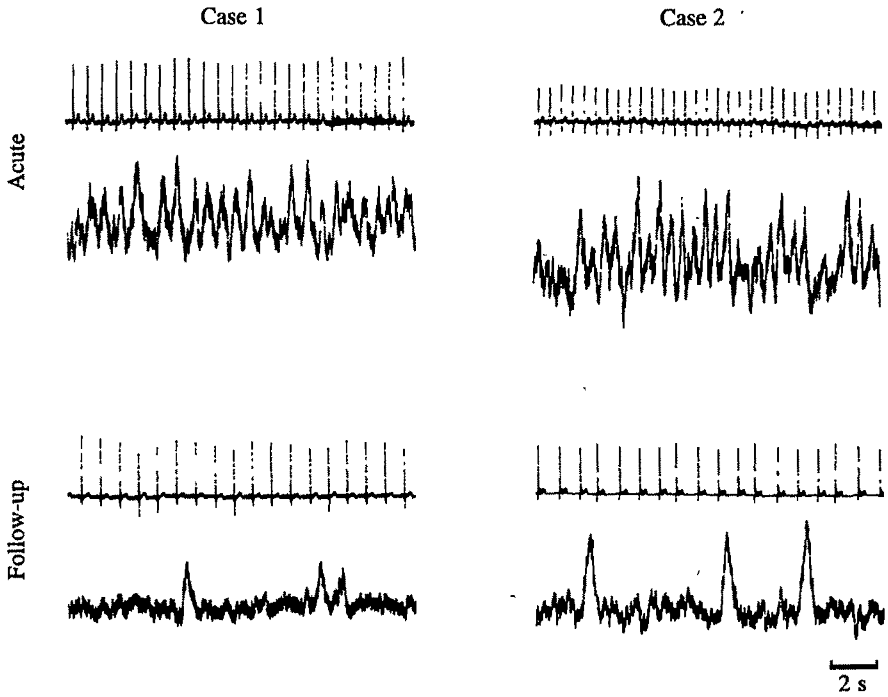

FIG. 1. ECG (*upper tracings*) and mean voltage neurogram (*lower tracings*) in the acute phase and at first follow-up recording of Cases 1 and 2. Note high number of sympathetic bursts with preserved pulse synchrony in the acute phase. Same time scale in all tracings.

TABLE. RESULTS OF MICRONEUROGRAPHIC RECORDINGS IN THE GUILLAIN-BARRÉ SYNDROME (GBS)

	Resting heart rate	*Burst/100 heart beats*	*Bursts/min*	*Reflex latency (s)*
1. GBS patients with clinical signs of sympathetic hyperfunction				
Case 1 Acute	97	83	80	1.43
Follow-up 1	72	16	12	1.28
Follow-up 2	58	24	14	1.36
Case 2 Acute	126	56	71	1.32
Follow-up 1	65	26	17	1.21
Follow-up 2	71	19	14	1.25
Case 3 Acute	100	64	64	1.30
Follow-up 1	85	37	31	1.17
Follow-up 2	62	42	26	1.24
2. GBS patients without clinical signs of sympathetic hyperfunction (GBS controls)				
Case A Acute	92	9	8	1.21
Follow-up	81	6	5	1.24
Case B Acute	62	63	39	1.22
Follow-up	66	54	36	1.23
Case C Acute	76	49	37	1.17
Follow-up	65	44	29	1.19
Case D Acute	79	33	26	1.43
Follow-up	61	42	26	1.34

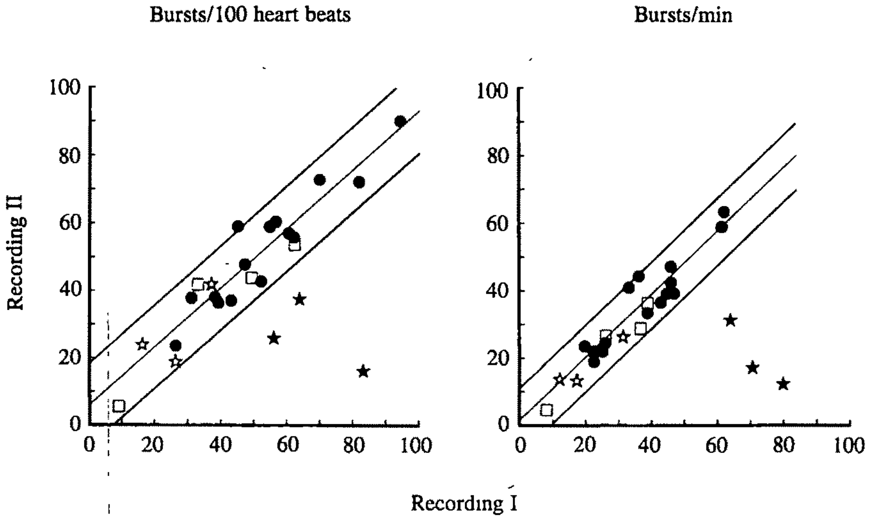

FIG. 2. Quantity of sympathetic bursts at two consecutive recordings plotted against each other ★ = GBS with tachycardia and hypertension; acute and first follow-up recording. ☆ = GBS with tachycardia and hypertension; both recordings after recovery. ☐ = GBS without autonomic involvement. ● = Healthy subjects. Thick lines indicate ±2 SD from the regression line. r = 0.94 for both graphs. Note clear aberration of the three GBS patients with hypertension and tachycardia at the recording during their acute illness.

tachycardia. However, during the first recording in Case 3, two brief episodes occurred when the pulse synchrony was lost and short sequences of bursts occurred in a rhythm which was slower than the cardiac rhythm (fig. 3, *right*).

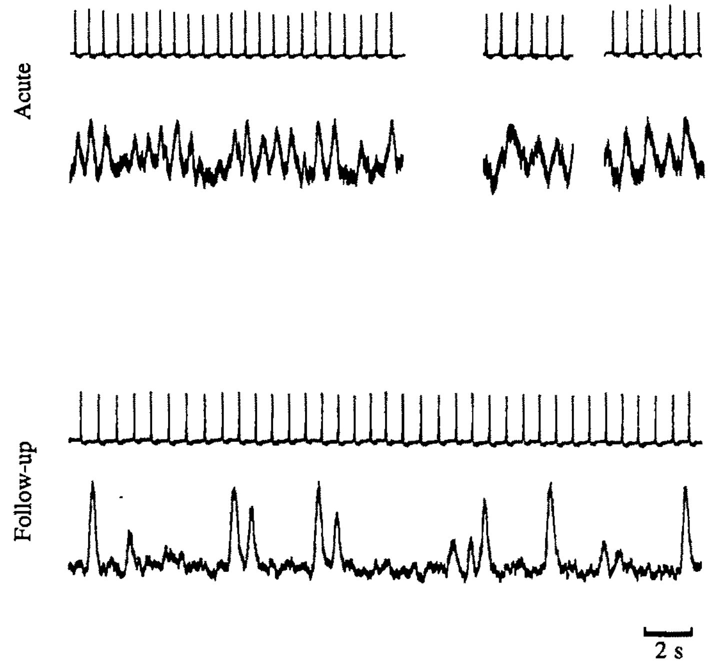

FIG. 3. ECG (*upper tracings*) and mean voltage neurogram (*lower tracings*) in the acute phase and at first follow-up recording of Case 3. High sympathetic outflow usually with maintained cardiac rhythmicity (*left part of acute recording*); note two brief episodes with bursts of activity without time-locking to heart rate (*right part of acute recording*). Same time scale in all tracings.

Mean sympathetic reflex latencies varied between recordings with somewhat longer latencies during the acute phase in patients with hypertension and tachycardia (*see* Table), but fell within normal range on every occasion (*see* Fagius and Wallin, 1980*a*). For the short sequences with loss of cardiac rhythmicity reflex latency could not be defined, as correspondence between heart beats and bursts was lacking.

During the acute illness when tachycardia was present heart rate variations were small. In Cases 1 and 3 burst durations were similar during the acute phase and after recovery. In Case 2, who had the most pronounced tachycardia in the acute phase, longer burst durations were seen after recovery (fig. 1, *right*). Mean burst durations in the acute and first follow-up recording for Cases 1, 2 and 3 were 0.50 s and 0.54 s, 0.44 s and 0.63 s, 0.52 s and 0.49 s, respectively. At follow-up recordings (and in the controls) burst durations had an approximately Gaussian distribution (fig. 4). However, during the acute recording in Cases 1 and 2 some bursts had about twice

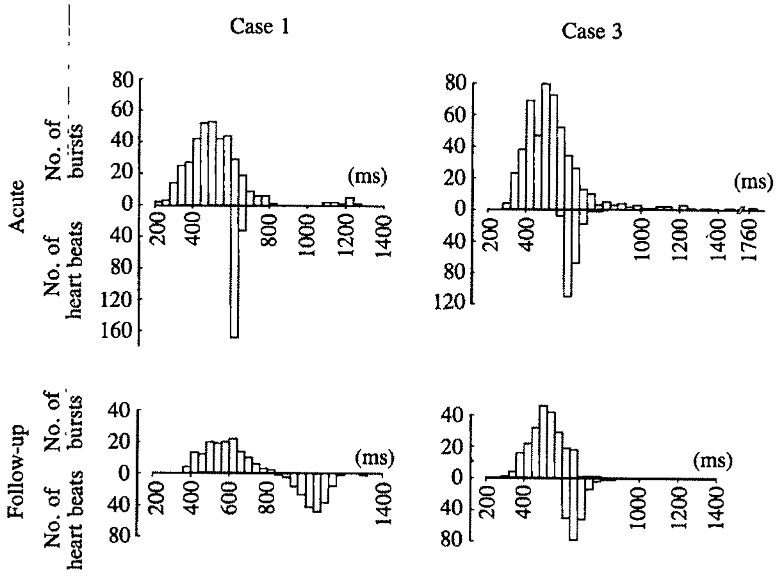

FIG. 4. Distributions of MSA burst durations and R-R intervals in Cases 1 and 3 during acute phase and at first follow-up recording. Note small amount of bursts with duration around 1,200 ms in acute recording of Case 1 and continuum of burst durations up to 1,400 ms in acute recording of Case 3. Number of bursts: Case 1 acute, n = 385 (5 min analysed); follow-up, n = 145 (15 min analysed). Case 3 acute, n = 502 (8 min), follow-up, n = 221 (8 min). R-R intervals: n = 200 in all histograms

the ordinary duration whereas during the acute recording in Case 3, durations were more variable with a continuum of bursts with longer durations (fig. 4).

There was no correlation between reductions of blood pressure and heart rate between recordings 1 and 2 and corresponding reduction of sympathetic activity. Thus Case 1 had the least pronounced hypertension and tachycardia but showed the greatest inter-recording difference in sympathetic activity (*see* Table).

The skin sympathetic effector organ tests were normal in Case 1, whereas Cases 2 and 3 had weak sudomotor but normal vasoconstrictor responses during the acute illness. At follow-up both responses were normal in all patients.

DISCUSSION

Although no confirmatory tests were undertaken in the present experiments, there was no doubt as to the sympathetic origin of the rhythmic neural bursts synchronous with the pulse. The pattern of activity with multiunit discharges occurring in the cardiac rhythm and waxing and waning in strength with shorter or longer interposed silent periods is highly characteristic. There is clear evidence of the sympathetic nature of this activity in healthy nerves (Vallbo *et al.*, 1979) and no reason to believe that the origin should be different in the Guillain-Barré patients. The only cardiac-linked activity that might possibly be misinterpreted as sympathetic would be afferent impulses from a mechanoreceptor situated close to an intramuscular pulsating vessel. Such discharges may occur (McKeon and Burke, 1981), but they show single unit characteristics and occur as one or two impulses repeated monotonously with each heart beat. In addition, the discharges may be influenced by mechanical stimulation of the muscle harbouring the receptor.

Level of activity

In the GBS patients with clinical signs suggesting sympathetic hyperfunction the level of muscle sympathetic activity was considerably higher during the acute phase than at follow-up. In contrast the two control groups had reproducible levels at the two recordings, confirming the findings of Sundlöf and Wallin (1977) that a given individual normally has a reproducible level of activity. The parallelism between clinical picture and level of sympathetic activity suggests that in the three GBS patients there was a temporarily elevated level of sympathetic activity during the acute illness rather than a decrease after the disease from a previously stable high level. The present findings provide the first direct evidence that some GBS patients have a temporarily increased sympathetic outflow during the acute phase of the disease. The result agrees with the suggestions of Lichtenfeld (1971) and Durocher *et al.* (1980), who based their conclusions on the clinical picture and haemodynamic findings. In healthy subjects there is a positive correlation between resting levels of MSA and plasma concentrations of noradrenaline (Wallin *et al.*, 1981) and therefore the finding of increased urinary catecholamine excretion in GBS with tachycardia and hypertension (Mitchell and Meilman, 1967; Davies and Dingle, 1972; Davidson and Jellinek, 1977; Durocher *et al.*, 1980) may reflect in part an increased sympathetic outflow to muscles.

The Character of the Sympathetic Activity

Durations of sympathetic bursts were similar (or slightly shorter) during the acute phase when activity was high and during follow-up when fewer bursts occurred. In healthy subjects confluence of two successive bursts may occur at high heart rates (B. G. Wallin and J. Fagius, unpublished data) and the bursts with double duration seen in Cases 1 (fig. 4) and 2 probably were confluent bursts. In Case 3, however, some bursts had durations that could not be interpreted as multiples of ordinary burst duration (fig. 4) and furthermore aberrations from the cardiac rhythmicity also occurred (fig. 3). These two findings suggest impairment of dynamic baroreflex mechanisms in Case 3.

The question may arise as to whether the short episodes of noncardiac linked discharges could have originated from injured myelinated nerve fibres rather than from sympathetic C fibres. It seems highly unlikely that the appearance of a noncardiac linked rhythm should coincide with a pause in the sympathetic rhythm (which did not occur on other occasions). If the noncardiac linked discharges and the sympathetic rhythms were present simultaneously, interference between the two rhythms should be expected. No sign of such interference was observed (although clear interference occurred when rhythmic afferent mechanoreceptor discharges were evoked by muscle stretch).

Possible Sites of Dysfunction

Theoretically baroreflex function can be changed by a lesion of the efferent, central or afferent parts of the reflex arc. Increased sympathetic outflow from a lesion of efferent pathways implies paraesthesiae-like activity, which is not compatible with preservation of cardiac rhythmicity. Most likely efferent lesions would result in a decreased outflow, as shown in studies on polyneuropathies (Fagius and Wallin, 1980*b*; Fagius, 1982). The possibility of a CNS disorder (with increased central drive or decreased sensitivity to normal baroreceptor inhibiting influence) cannot be discarded, but all other manifestations of the disease were peripheral in all patients.

Damage to afferent pathways with diminished but not entirely absent baroreceptor inhibition might explain the present findings. Arterial baroreceptors and intrathoracic low pressure receptors affect the outflow of MSA differently. Thus, arterial baroreceptor influence (which is responsible for the grouping of the sympathetic impulses synchronous with the pulse) is mainly dynamic; for example, maintained stimulation of carotid baroreceptors in man causes only transient changes of MSA (Båth *et al.*, 1981; Wallin and Eckberg, 1982) and little or no maintained changes of forearm (mainly muscle) vascular resistance (Abboud and Mark, 1979; Lindblad *et al.*, 1982). In contrast, unloading of intrathoracic low pressure (volume) receptors by application of subatmospheric pressure around the lower body increases MSA (without affecting the pulse synchrony) (Sundlöf and Wallin, 1978*b*) and forearm vascular resistance (Abboud and Mark, 1979) for as long as the stimulus is maintained. In view of these reflex properties a decreased afferent inflow from volume receptors with preserved arterial baroreceptor function may give rise to an increased sympathetic outflow with maintenance of pulse synchrony. A superimposed defect of arterial baroreceptor afferent activity could account for loss of cardiac rhythmicity in the sympathetic activity. Since in Case 3 pulse synchrony was lost only episodically the defect was probably partial and perhaps variable. This would be in accordance with the findings of Davidson and Jellinek (1977) and Tuck and McLeod (1981) who reported partially depressed baroreflex function in patients with GBS and hypertension.

After complete baroreceptor denervation in the cat, splanchnic sympathetic activity was no longer time-locked to the cardiac rhythm but still occurred in rhythmic bursts of similar rate as before denervation (Gebber, 1980). From such findings Gebber postulated the existence of an intrinsic central sympathetic rhythm with a frequency similar to the heart rate and normally entrained by pulsatile input from the baroreceptors. If, in the present study, arterial baroreceptor activity was abnormally weak in Case 3, the bursts occurring when pulse synchrony was lost may represent an intrinsic central sympathetic rhythm.

Functional Importance of Increased Sympathetic Outflow

The role of the increased muscle sympathetic activity for the hypertension in the GBS patients is difficult to assess. There was no quantitative correlation between the blood pressure increase and the degree of sympathetic hyperactivity. Previous studies have shown that neither in healthy nor in hypertensive subjects is there a significant relationship between levels of MSA and blood pressure (Sundlöf and Wallin, 1978*a*; Wallin and Sundlöf, 1979). Furthermore, the increase of MSA during application of lower body negative pressure is not accompanied by significant changes of arterial blood pressure (Sundlöf and Wallin, 1978*b*) and neither is there a significant relationship between clonidine-induced changes of arterial blood pressure and MSA. In view of such findings it seems unlikely that the increased blood pressure level seen in the GBS patients should be caused solely by the increased level of MSA. More probably the blood pressure increase is due to the added effects of tachycardia and enhanced sympathetic outflow to muscles and presumably also to other baroreflex controlled vascular beds.

In normal resting man, the quantity of MSA differs remarkably between individuals, the range being from less than 10 to more than 90 bursts/100 heart beats (Sundlöf and Wallin, 1977). It seems likely that this reflects interindividual differences in cardiovascular homeostatic mechanisms which are poorly understood. Compared to a subject with high sympathetic burst incidence, a subject with low burst incidence when healthy should have greater opportunities for increasing his sympathetic drive on muscle vessels in pathological states. It is unclear whether this means that subjects with low sympathetic burst incidence when healthy are more likely to develop significant hypertension if they acquire the Guillain-Barré syndrome. It is interesting to note, however, that when recovered from autonomic symptoms, all 3 GBS patients in the present study indeed had fairly low incidences of sympathetic bursts in muscle nerves.

Skin sympathetic discharges were not recorded in the present cases. Weak sudomotor responses in 2 cases suggest a decreased skin sympathetic outflow. A skin sympathetic hypofunction and at the same time excessive muscle sympathetic outflow are not contradictory findings. The pathophysiological mechanism suggested above for an increased sympathetic activity, with a lesion to afferent fibres from some of the baroreceptors, is valid only for an inhibitory reflex. Cutaneous sympathetic responses to arousal stimuli are due to an excitatory reflex and since the patients felt and heard the stimuli the afferent pathways must have been intact. Thus in most cases abnormal skin sympathetic activity will be due to a lesion of efferent fibres and decreased function is most likely to occur. However, spells of hyperhidrosis have been reported in the GBS (Lichtenfeld, 1971) and transient profuse sweating has been seen in patients with acute pandysautonomia (Hopkins *et al.*, 1974). In such cases an increased central drive or mechanisms akin to paraesthesiae may be present.

Sudden death, presumably due to 'circulatory failure', may occur in GBS patients with clinical signs of sympathetic hyperactivity and may nowadays even be the most important cause of fatal outcome in GBS (Lichtenfeld, 1971; Davidson and Jellinek, 1977). In normal subjects a parallelism between muscle sympathetic activity and autonomic influence on the heart can be demonstrated (Wallin and Nerhed, 1982). The present demonstration of a marked increase of muscle sympathetic activity may indicate that β-blocking treatment may be of vital importance when tachycardia and hypertension occur in the Guillain-Barré syndrome.

ACKNOWLEDGEMENTS

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MOTOR ACTIVITY AND MUSCLE PROPERTIES IN THE HEMIDECEREBELLATE CAT

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SUMMARY

Luciani's ipsilaterally acting 'trophic' cerebellar influence on striated muscle was reinvestigated in hemidecerebellate preparations of varying extent. Cats with hindlimb postural asymmetries for 4 or more days after the lesion developed a bilateral reduction of maximum tetanic tension and increased twitch/tetanus ratios of soleus. In addition, soleus on the side of the lesion lost force and weight, showed decreased twitch contraction and half-relaxation times, elevated myosin ATPase activity in part of its fibres, occasional fibre necrosis and a few snake coils.

Protracted postural asymmetry occurred only if complete hemicerebellectomy included ablation of the lateral vestibular nucleus and extended for at least 3.0 mm across the midline into the contralateral vermal and intermediate cortex, especially of Larsell's lobuli IV and V. Most simply, the cerebellar effect on muscle is explained as the result of altered motoneuronal activation patterns.

Comparison of the experimental soleus changes with Holmes's clinical findings in cases of cerebellar injury suggests that muscle itself participates in experimental and human cerebellar asthenia.

INTRODUCTION

Whether cerebellar lesions affect limb muscle properties is uncertain, how they may do so is unknown. In hemidecerebellate preparations Luciani (1893) originally attributed pallor and thinning of striated muscle to loss of an ipsilaterally acting trophic influence. Patrizi (1906) and Krestownikoff (1928) confirmed his findings, but Dusser de Barenne (1937) found normal muscle contractility in hemidecerebellate cats, questioned the older data and called for additional experiments. Although Holmes (1917) has settled beyond doubt that cerebellar lesions may reduce voluntary strength in man, the question whether muscle itself participates in 'cerebellar asthenia' has remained open.

To answer this question and gain some insight into the means whereby lesions of a motor metasystem (Mackay and Murphy, 1979) may impair limb function, we decided to reinvestigate the effect of hemicerebellectomy on cat soleus muscle. Such a lesion may affect muscle by changing motoneuronal firing patterns, altering the autonomic nervous outflow, impeding the release of discharge-independent trophic factors, or by leading to poor nutrition, infection and pressure sores.

Our results will demonstrate that cerebellar lesions affect the soleus in proportion to the duration of the resulting asymmetric hindlimb posture. Muscle changes occur only upon ablation of more than half the cerebellum. Postoperative behaviour and electromyography (EMG) will disclose that muscle changes are related to disuse, most simply explained as the effect of altered motoneuronal activation. Decrease of the maximal soleus force implies that muscle itself participates in cerebellar asthenia. Some of the findings have been presented at a meeting (Stenvers *et al.*, 1977).

METHODS

Experiments were performed on 38 adult cats weighing 2.5 to 5.3 kg. Under general anaesthesia the left side of the cerebellum was removed by suction in 23 animals. They were studied postoperatively for two to three weeks. Cats lay on plastic-lined diapers over a thick layer of sawdust. None developed pressure sores. Also under general anaesthesia, the properties of both solei were examined in a final acute experiment. The solei and their nerve supply were dissected free and covered with liquid paraffin at 38 ± 1 deg C. The femur and tibia were rigidly fixed by heavy clamps and the soleus tendon attached to an isometric force transducer. The muscle was stretched to the minimum length at which the twitch had its maximum amplitude, and activated by supramaximal 0.1 ms pulses delivered to the cut motor nerve. Measurements were made of the single twitch and the maximum tetanic tension. The latter was produced during a 0.5 s burst of repetitive activation and typically reached its maximum at stimulus frequencies of 100 to 200 Hz.

Upon completion of these measurements, the solei were removed, blotted and weighed. Transverse slices were frozen in isopentane cooled by liquid nitrogen and were then stored at −96° C for histochemical study. Transverse and longitudinal 6 μm sections were cut at −30° C and stained for myosin triphosphatase (ATPase; EC 3.6.1.3), glycerol-3-phosphate: menadione oxidoreductase (GPOX; EC 1.1.99.5), NADH: tetrazolium oxidase (NADH; EC 1.6.99.3) and succinate dehydrogenase (SDH; EC 1.3.99.1) as described before (Meijer and Elias, 1976). For morphology, sections were also stained with haematoxylin and eosin.

EMG recordings were obtained from the soleus and lateral gastrocnemius muscles in 3 hemidecerebellate cats, through teflon-coated nichrome wires which had been implanted two to three weeks before operation. Muscles with implanted electrodes were not used for contractility studies. The electrodes were bipolar and had bare tips of about 0.4 mm. At the amplification levels used there was no cross-talk in the recordings between adjacent gastrocnemius and soleus muscles.

Since cerebellar autonomic effector responses are mediated by the fastigial nuclei (Achari and Downman, 1970), we destroyed the rostral or caudal part of one fastigial nucleus stereotactically by electrolytic coagulation, using a modified Horsley-Clarke technique and the Berman (1968) atlas. Because the 3 animals with rostral fastigial and the 3 with caudal fastigial lesions had normal soleus measurements, we used these animals in addition to 9 normal cats as controls.

Mean body weight did not differ significantly between the 15 control (3.4 ± 0.7) and 20 hemidecerebellate cats (3.1 ± 0.8 kg). In the control animals, muscle measurements from the left and right sides did not differ. In each of the 9 normal cats the average of measurements from the two sides was used for further calculation (figs. 3, 4).

Differences between mean data from normal and hemidecerebellate cats were analysed with the aid of the t-test for independent samples. Differences between corresponding left and right side muscles were judged by means of the Wilcoxon matched-pairs signed ranks test.

At the end of experiments, cats were perfused with 10 per cent formalin and the brains were removed. The extent of the cerebellar and brainstem lesions was determined in serial paraffin sections, cut in the frontal plane and stained according to the technique of Klüver-Barrera. Lesions were reconstructed in the frontal plane and then transferred to standard anterior and dorsoventral views of the cerebellum (fig. 2).

RESULTS

Duration of the Motor Deficit vs Extent of the Lesion

Postoperatively, 18 of the 20 animals preferred to lie on the left; if placed on their right flank they would immediately turn back to the left, initially often after a series of violent rolls. Rolling was quite prominent in 2 cats whose left eighth nerves had, together with the cerebellar peduncles, inadvertently been cut. For ten and twelve days respectively, these animals alone preferred to lie on their right side with both hindlimbs flexed. In the 18 other cats, one to three days after operation a rather persistent posture would arise (fig. 1) with mild opisthotonus of the neck, forelimb extension especially on the left, hypotonic semiflexion of the left and active extension of the right hindlimb. Myotatic reflexes were less on the left. The extended right hindlimb showed a positive clasp-knife phenomenon. In EMG recordings the left soleus was silent (fig. 1, left), the right persistently active (fig. 1, right).

Head motility and forelimb function recovered first, head righting mostly within two days. With active movements, ataxia and intention tremor of the head and left forepaw appeared together. Contact placing and supporting reactions were slightly depressed in the right, and virtually absent in the left limbs. There was no hopping or buttressing of the limbs, nor righting reflexes from the body on the left.

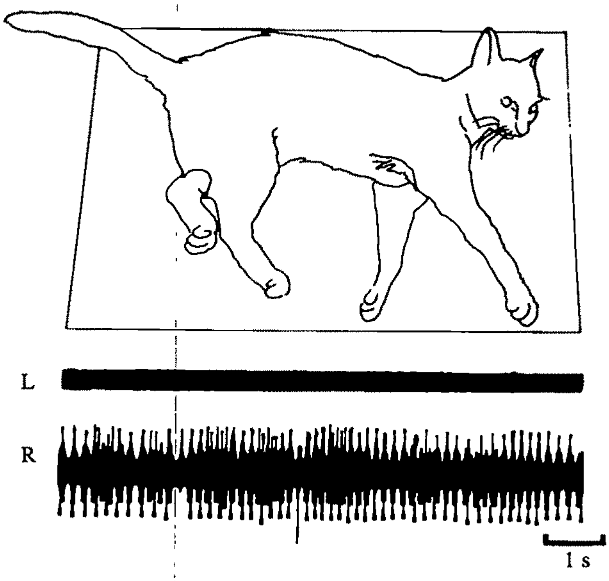

FIG. 1. Characteristic posture following a left hemidecerebellation. *Bottom:* EMG of flaccid left (L) and rigid right (R) solei recorded through indwelling electrodes on the seventh day postoperatively, amplitude 1.2 to 1.5 mV.

Speed and degree of the postoperative recovery depended on which cerebellar structures had been ablated. The asymmetric hindlimb posture (fig. 1) lasted up to one day in 3, four to seven days in 5, and nine to fourteen days in 10 cats. The 3 animals with postural asymmetry of no more than one day were standing and walking with left hemiataxia and hypermetria within two to five days after the lesion

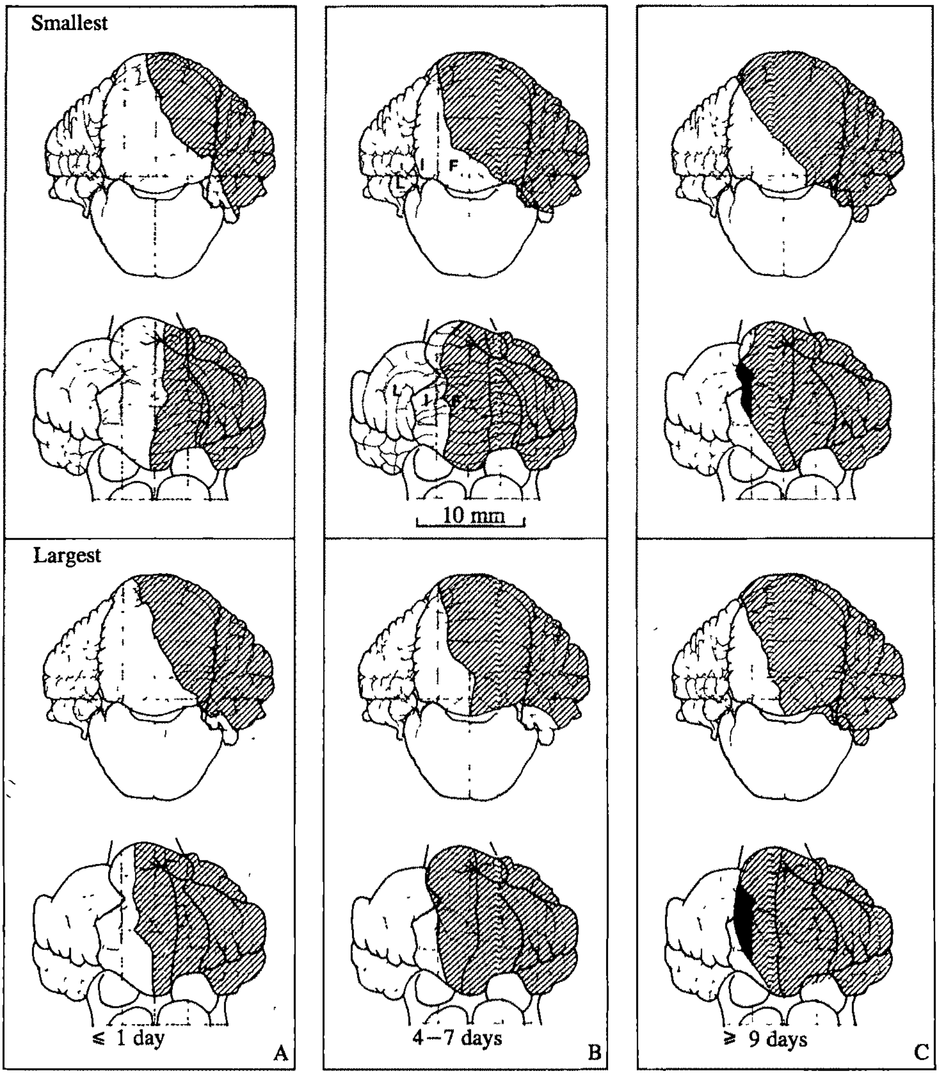

FIG. 2. Topography of six characteristic lesions *vs.* duration of the asymmetric hindlimb posture. The extent of each lesion is indicated by shading on standard anteroposterior and dorsoventral views of the cerebellum. The lateral (L), interpositus (I) and fastigial (F) nuclei have been drawn in dotted outline. Interrupted straight lines indicate the stereotactic planes horizontal 0.0, lateral +3.0, 0.0 and −3.0 mm. Vertically, the columns demonstrate incomplete (A), complete (B) and extended (C) hemidecerebellations. The period of postoperative asymmetric hindlimb posture is indicated at the bottom of each column. Horizontally, the top rows of reconstructions show the extent of the smallest, the bottom rows the size of the largest lesion in each group. The cortical areas whose removal prolongs asymmetric posture to nine days or more are indicated in black.

date. Their hemicerebellectomies appeared incomplete (fig. 2A) and microscopically the Deiters' nuclei were intact. The normal physiological measurements from their solei are represented by filled circles in fig. 4. Soleus histochemistry gave the same results as in normal cats.

None of the 5 animals with postural asymmetries lasting four to seven days regained the ability to stand or walk. Reconstructions of their lesions are illustrated in fig. 2B, and measurements from their solei given in fig. 4, open circles. Of the 10 cats with asymmetric hindlimb posture for ten to fourteen days, only 2 ever managed to stand for a few moments or walk a few steps if supported from the left. In the group of 15 animals with a postural asymmetry of more than four days (figs. 2B, C), body weight had decreased by 15 ± 8 per cent at the time of the acute experiment.

It appears that protracted asymmetries occur only if, besides the left hemicerebellum, the right vermal and intermediate cortex of Larsell's (1953) lobuli I to VI were ablated, the lesion extending across the midline beyond the sagittal plane through the medial border of the right anterior interpositus nucleus (fig. 2C). The removal of the right intermediate cortex of lobuli IV and V (fig. 2C, black areas) is critical. Microscopically, the lesions of figs. 2B and C had invariably destroyed the origin of the left lateral vestibulospinal projection to the limbs, leaving at most some pyknotic and hyperchromatic cells of the left ventral Deiters' nucleus. The origin of the pontomedullary reticulospinal fibres, comprising the medial two-thirds of the reticular formation (Torvik and Brodal, 1957) and the more laterally situated pontobulbar motor strip (Mori *et al.*, 1980), had been spared in all cases.

In contrast with the critical significance of the cortical and lateral vestibular lesions, the degree of fastigial damage appears unimportant. Sparing or ablation of the right fastigial nucleus had no influence on the behaviour of the 15 cats of fig. 2B and C. Furthermore, the 6 control animals with stereotactic fastigial lesions maintained their body weight postoperatively. During the entire survival period, the 3 animals with cranial fastigial lesions tended to fall to the left, the 3 with caudal fastigial lesions had a slight tendency to stagger to the right. The acute experiment disclosed normal soleus weight and contractility. Microscopically, destruction of the left cranial fastigial nucleus was associated with a moderate amount of cell loss in both caudal fastigii; the lesions of the left cranial and caudal fastigii were complete.

Duration of Postural Asymmetry vs Muscle Change

If hindlimb posture had been asymmetrical for at least four days, as was the case in 15 cats, the acute experiment on the solei of both limbs showed a loss of maximum tetanic tension (fig. 3A) and an increase of the twitch/tetanus ratio (fig. 3D). In addition, comparison of the left and right solei disclosed four significant side differences: asymmetry of force and weight, asymmetry of twitch speed, and asymmetry of histochemical staining for myosin ATPase. Both cats that postoperatively remained on their right side with symmetrically flexed hindlimbs ended with symmetrical soleus contractility and weight.

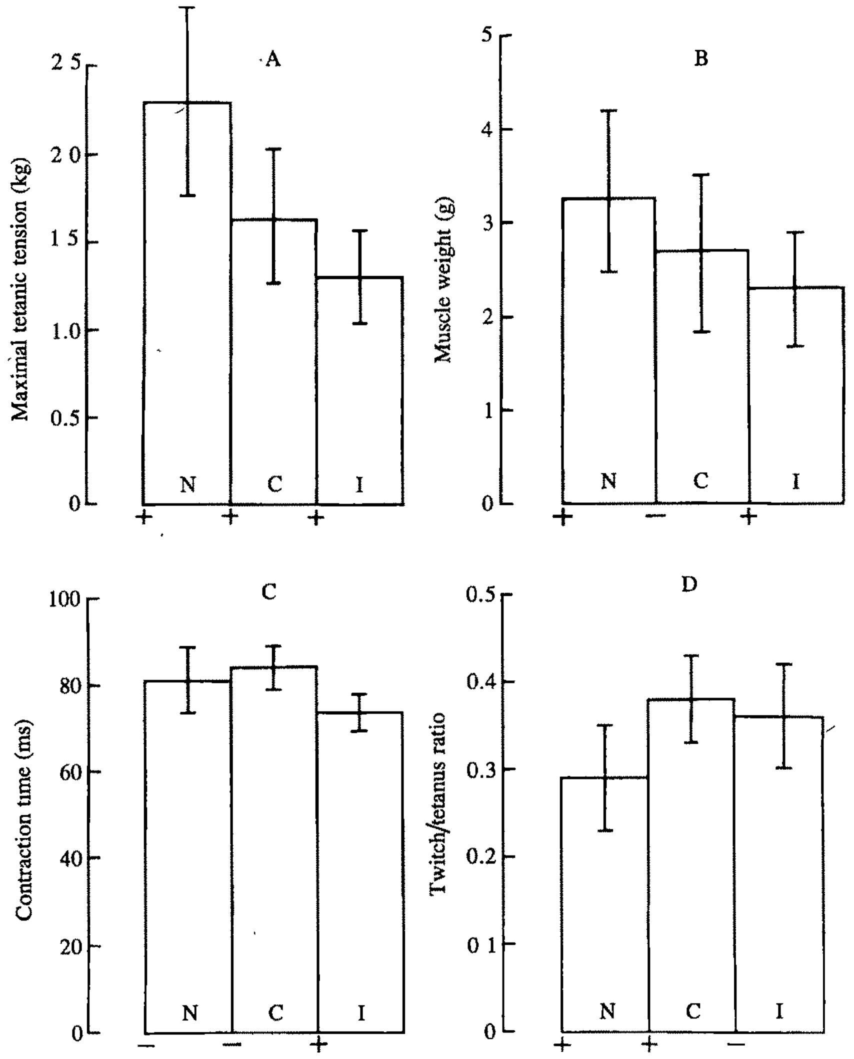

Fig. 3. Properties of soleus muscle in 9 normal (N) and 15 hemidecerebellate cats with at least four days of hindlimb postural asymmetry, contralateral (C) and ipsilateral (I) to the lesion. Of each column the top represents the average value, the vertical bar ±SD. A represents maximum force, B, weight, C, contraction time and D, the twitch/tetanus ratio. Statistical significance (between columns N and C or I by the t-test, between C and I by the Wilcoxon test) of at least $P < 0.05$ is indicated by +, its absence by –. Signs at the bottom left corner of the N columns indicate differences between the columns N and I. All other signs show differences between adjacent columns.

Force and weight. At the time of the acute experiment the solei had a normal florid colour but appeared weaker (fig. 3A) and smaller (fig. 3B) than normal muscles. The passively lengthened left solei (fig. 3A, B) were more affected than the actively shortened right muscles. The asymmetries of soleus force (fig. 4A) and weight (fig. 4B) increased with the period of asymmetrical posture.

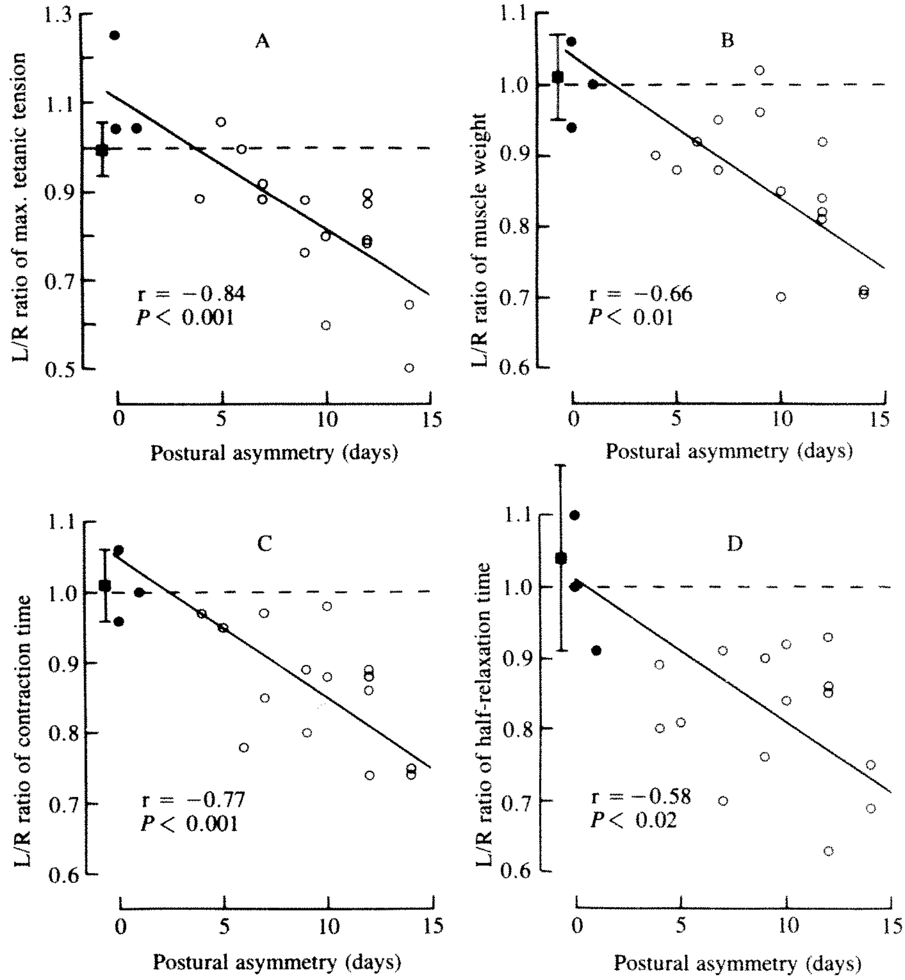

FIG. 4. Left/right ratios of soleus properties *vs* duration of postural asymmetry. Ratios of maximum tetanic tension in A, muscle weight in B, contraction time in C, and half-relaxation time in D. ■ = normal; bar ± SD (n = 9). ● = incomplete lesions as in fig. 2A (n = 3). ○ = complete and extended lesions as in fig. 2B, C (n = 15). Correlation coefficients and corresponding P values for n = 18 are in the figure. If one discards the 3 incomplete lesions and only considers the 15 complete and extended lesions, the r and P values are: A, r = −0.54, $P < 0.05$; B, r = −0.57, $P < 0.02$; C, r = −0.55, $P < 0.05$; D, r = −0.24, P not significant.

In normal cats the ratio of soleus to body weight is $(1.0 \pm 0.21)0.10^3$ (n = 9). The acute experiment disclosed that the left soleus had lost weight in excess of the general postoperative loss of body weight: the soleus to body weight ratio had significantly fallen to $(0.79 \pm 0.12)0.10^3$ on the left ($P < 0.02$), and was unaffected (0.93 ± 0.15) 0.10^3 on the right.

Twitch contraction and half-relaxation times. Individual solei of hemidecerebellate cats had normal contraction and half-relaxation times. Very significant differences occurred, however, between the contraction times of left and right solei in hemidecerebellate cats (fig. 3C) and increased with the period of asymmetric posture (fig. 4C, D). Similarly, half-relaxation times of left and right solei differed and were 88 ± 15 and 109 ± 18 ms, respectively. The statistical levels of significance relative to normal soleus half-relaxation time (101 ± 25 ms) are the same as those given for contraction times in fig. 3C.

Because the twitch/tetanus ratios of left and right solei did not differ significantly (fig. 3D) the asymmetries of contractility are not secondary to asymmetrical changes in series elasticity (Close, 1972).

Myosin ATPase. Normal soleus, almost exclusively composed of slow twitch fibres (McPhedran *et al.*, 1965), showed the expected uniform light staining for myosin ATPase. In GPOX sections, about 80 per cent of the fibres had medium, the remainder high activity. All fibres stained darkly in NADH and SDH preparations.

In some solei of hemidecerebellate animals, myosin ATPase histochemistry revealed a smaller or greater number of darkly stained fibres. The left solei from 4 animals with large lesions (fig. 2C) showed a diffuse heterogeneous staining pattern (fig. 5) resembling that of a mixed hindlimb muscle; about 10 per cent (418/4000) of the fibres stained darkly. Smaller numbers of darkly stained fibres were seen in some muscle specimens equally on the left as on the right. All muscles showed a normal staining pattern for GPOX. Additional NADH and SDH sections, made in half of the solei from hemidecerebellate cats, demonstrated the same uniform high activity as normal specimens. Histology of the left solei disclosed a few centrally located

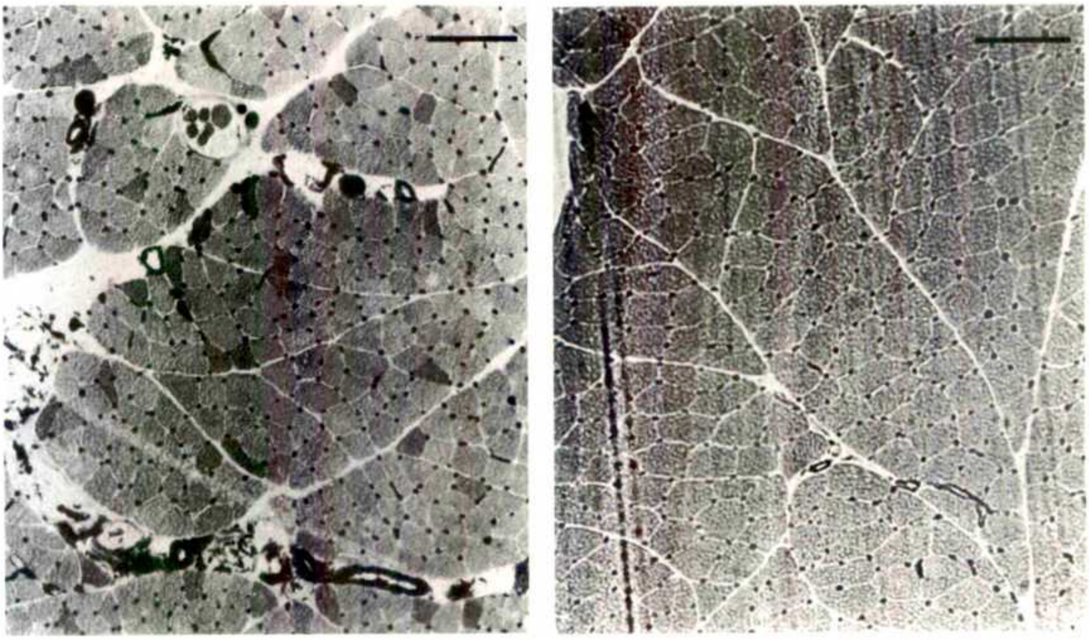

FIG. 5. Altered myosin ATPase activity of soleus ipsilateral to an extended hemidecerebellation. *Left*, elevated activity of about 10 per cent of the left soleus fibres. *Right*, normal uniform light staining pattern of right soleus. Cerebellar lesion as in fig. 2C. Bar = 100 μm.

sarcolemmal nuclei, occasional necrotic fibres and some snake coils (Karpati and Engel, 1968). The right solei were microscopically normal.

DISCUSSION

Our main finding is that the withdrawal of Luciani's 'trophic cerebellar influence' depends on altered motoneuronal discharge patterns. Muscle appears to change in direct proportion to the duration of asymmetrical limb posture which, in turn, depends upon lesion topography: only if the left lateral vestibular nucleus and at least a 3.0 mm wide strip of right vermal and intermediate cortex are ablated do protracted postural asymmetries occur. Such lesions mainly disrupt descending facilitation that arises in the lateral vestibular, the red, and the mesencephalic reticular nuclei. Ablation of the left dorsocaudal Deiters' nucleus completely abolishes the lateral vestibulospinal projection to left soleus extensor motoneurons. Removal of the narrow vermal cortical zone where the direct inhibitory cerebello-vestibular fibres originate (Corvaja and Pompeiano, 1979; Ito *et al.*, 1968; Voogd and Bigaré, 1980) facilitates the right nucleus of Deiters. The opposite effects of the lesion on the left and right Deiters' nuclei therefore result in strongly diminished left and mildly diminished right soleus postural contractions. The left hindlimb flexors are flaccid from disfacilitation of the right red nucleus following the removal of the entire left nucleus interpositus (Pompeiano, 1967).

The effects from the mesencephalic reticular formation are more complicated, because cerebellar stimulation has yielded limb flexion and extension from closely adjacent areas. However, Pompeiano (1958) has obtained active ipsilateral limb flexion on stimulating the paravermal intermediate cortex. Also, destruction of the intermediate cortex of lobuli IV and V (Ito *et al.*, 1964; Brodal, 1967) may have disinhibited the right caudomedial interpositus nucleus, where Maffei and Pompeiano (1962) have elicited ipsilateral limb extension. Such interpositus disinhibition would have increased right soleus extension in our experiments.

As a result of diminished motoneuronal activation, the physiological and histochemical properties of the left solei change to the same amount: twitch contraction times are about 12 per cent shorter on the left than the right (fig. 3A) and elevated myosin ATPase is present in about 10 per cent of the left soleus fibres. This confirms Bárány's (1967) finding that myosin ATPase activity increases with the speed of muscle shortening. The presence of snake coils in disused solei corroborates Karpati and Engel's (1968) observation that they are a sign of neurogenic disease. Hemicerebellectomy is comparable to most disuse models in mainly affecting slow twitch muscle (Vrbová *et al.*, 1978). For instance, following transection of the cord, cat soleus muscle acquires several properties characteristic of fast twitch muscle (Edgerton *et al.*, 1980) and the same changes occur in denervated rat soleus muscle if stimulated at high frequencies (Lømo *et al.*, 1980). The latter results accentuate the importance of the pattern of muscle activation, since rat soleus does not speed up following denervation without stimulation.

Our results eliminate several possible mechanisms of the cerebellar effect on muscle: it is not carried by the autonomic system because autonomic signals leave the cerebellum through the fastigial nuclei (Achari and Downman, 1970). Muscle changes are lacking in our cats with fastigial lesions and occur regardless of sparing or ablation of the right nucleus fastigii. Since both cats that remained postoperatively on the right side had symmetrical solei, habitual recumbency on the left does not explain our findings. The effects of passive stretch would have counteracted the actual weight loss of the left soleus (Burešová *et al.*, 1969; Gallego *et al.*, 1979). The symmetrical twitch/tetanus ratios (fig. 3D) prove that the asymmetrical soleus changes did not result from altered series elasticity (Close, 1972).

Despite a lack of accurate information on the topography of their lesions we may suppose that Patrizi (1906) and Krestownikoff (1928) have reported muscle changes following the removal of more than half the cerebellum, whereas Dusser de Barenne (1937) may have obtained negative results in more precisely hemidecerebellate preparations.

The disuse changes of soleus are elements of cerebellar asthenia defined by Holmes (1922) as a deficiency in the energy of voluntary, automatic and reflex actions. On cerebellar injuries he remarks: 'Although it is immediately after the onset of acute lesions that this asthenia is usually found, my notes on several warfare injuries indicate that, like atonia, it may increase during the first week or two after the infliction of the wound.' The average ratios of the ipsilateral/contralateral muscle dynamometer readings in his two cases of unilateral injury are 0.63 and 0.73. These values agree well with the maximum tetanic tension ratios of the solei at fifteen days (fig. 4A).

The present experiments strengthen our earlier observation (Eerbeek *et al.*, 1982) that some motor effects of cerebellar lesions reside in the affected limb muscles. Since weakness developed to a similar degree and about as rapidly in Holmes's cases as in the solei of our cats, the secondary posttraumatic increase of human cerebellar asthenia may also reflect disuse of muscle.

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DRAWING OBJECTS FROM MEMORY IN APHASIA

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SUMMARY

The ability of aphasic patients to draw from memory objects with a characteristic shape has been investigated. Their capacity to reproduce the form of real objects was studied by showing them for a short time line drawings of simple objects. When the patient had analysed and recognized the figure, the model was hidden from view and the subject was asked to draw the same object from memory. This Drawing from Memory task was administered to 54 aphasics, 67 patients with right hemisphere lesions, 44 nonaphasic left brain-damaged patients and 23 normal controls. The influence of visuoconstructive disabilities was controlled by administering to the same patients a standard test for constructional apraxia (copying 10 geometrical figures). The severity and clinical form of the aphasia and the presence of semantic-lexical impairment at the receptive level were also examined in the aphasic patients. The following results were obtained. (1) Aphasic patients scored significantly less well than the control groups on the Drawing from Memory task and the intergroup differences became greater when the scores from the test for constructional apraxia were included by an analysis of covariance. (2) No significant correlation was detected between the severity and clinical form of the aphasia and the scores obtained on the Drawing from Memory task. (3) There was a significant correlation between impaired drawing from memory and disruption at the semantic-lexical level of language integration.

INTRODUCTION

In recent years several investigations have shown that aphasic patients may exhibit a variety of nonverbal disturbances in addition to their well-established linguistic disorders. It has been shown, for example, that these patients are often unable to recognize the source of a familiar nonverbal sound (Spinnler and Vignolo, 1966; Faglioni *et al.*, 1969), fail to understand the meaning of simple pantomimes (Duffy *et al.*, 1975; Gainotti and Lemmo, 1976), are unable to associate the form of an object with its colour (De Renzi *et al.*, 1972) and are severely impaired in tasks of abstract thinking (De Renzi *et al.*, 1966) and of conceptual judgement (Gainotti *et al.*, 1979). The meaning of these disturbances, however, remains controversial. Some authors (for example, Gainotti *et al.*, 1979) have claimed that a functional relationship exists between linguistic and extralinguistic disturbances. Other authors (*see* De Renzi *et al.*, 1966) have suggested that aphasia and nonverbal disturbances could be due to a lesion of anatomically contiguous but functionally independent cortical areas.

The aim of the present study was to assess whether aphasic patients are also impaired when they are requested to draw from memory the form of objects with a characteristic shape. Scattered observations on this subject already exist in the neuropsychological literature, but no systematic investigation has been undertaken to study this problem in a controlled experimental situation. Head (1926) and Bay (1962, 1964) noticed, for example, that aphasic patients are often unable to draw from memory objects having a characteristic shape (or to model them with plastic material). Bay, in particular, claimed that aphasic patients generally do not reproduce in their drawings (or models) those 'essential details' which are necessary for a clear and unequivocal identification of an object and attributed this to a basic conceptual disorder.

Further data pointing to a specific difficulty for aphasic patients to draw objects from memory was obtained by Duensing (1953), Piercy *et al.* (1960) and Gainotti *et al.* (1972), who showed that the presentation of a model to copy considerably improves the drawing ability of aphasic left brain-damaged patients, but does not facilitate the performance of right brain-damaged patients with constructional apraxia.

Other authors, however, objected to the concept of a specific impairment in aphasic patients for drawing objects from memory. They noted that painters affected by aphasia do not necessarily lose their artistic capabilities (Alajouanine, 1948; Gourevitch, 1967; Kornyey, 1977) and that patients with severe expressive aphasia can sometimes use their residual drawing abilities as a form of communication (Hatfield and Zangwill, 1974; Pillon *et al.*, 1980).

A critical discussion of the published data is rendered difficult by methodological inconsistencies in the previous studies. The capacity of aphasic patients to draw objects from memory has generally been studied in individuals or in very small groups of patients and investigated by uncontrolled clinical procedures. The performance of aphasic patients has not been compared with control groups of nonaphasic brain-damaged patients. No systematic attempt has been made to control the influence of associated variables, such as a defect of verbal comprehension (if the objects to be drawn had simply been named by the examiner) or the influence of constructional apraxia, which may have a deleterious effect on the performance obtained by aphasic patients in a drawing task.

The present study was therefore designed to clarify, in a more precisely controlled manner, the following issues. (1) Are aphasic patients significantly more impaired than right brain-damaged patients or left brain-damaged patients without any aphasia on a test of drawing objects from memory? (2) Is impaired drawing from memory in aphasic patients only a consequence of a more general visuoconstructional disorder or is this defect still evident when variance associated with constructional apraxia is removed? (3) Can a significant relationship be found between impaired drawing from memory and the clinical form of the aphasia, the severity of language disorder, and impairment at the semantic-lexical level of language integration?

MATERIAL AND METHODS

Testing Procedures

Drawing from Memory test. The capacity of aphasic patients to reproduce from memory the form of real objects was studied with a nonverbal procedure, namely, showing the patients for a short time line drawings of simple objects chosen because they have a characteristic shape. These objects were a nail, a pear, a key, an arrow, a glass, a comb, a cluster of grapes, a table, a hand and an umbrella. When the patient had analysed and recognized the object (usually by naming it), the model was hidden from view and the subject was asked to draw the same object from memory. The following score was given for each drawing: *2 points* if the object could be easily recognized with the drawing containing most of its characteristic details; *1 point* if the object contained only a few of its characteristic details but could still be recognized; *zero* if the object was not recognizable. Two independent judges evaluated all the drawings and the sum of their scores formed the 'drawing from memory score' obtained by each individual patient. Since the test consisted of 10 items and each drawing was evaluated by two judges, the maximum score obtainable was 40.

Copying drawings. To test for constructional apraxia, all patients received a test of copying geometrical drawings proposed by Arrigoni and De Renzi (1964). This test consists of 6 models, the last 2 of which are composed of 3 figures, so that a total of 10 geometrical drawings are presented to the subject to copy. For each patient the copy scored *2 points* for essentially correct reproduction, *1 point* if the copy was partly defective (omission of some lines, rotation, distortion or size errors) but not to such an extent as to prevent the identification of the figure, and *zero* for unrecognizable reproduction. As for the Drawing from Memory test, two independent judges evaluated all the copies and the sum of their scores formed the 'copying drawings score' for each patient. The maximum score obtainable was again 40.

Assessment of type and severity of aphasia. To study the relationship between impaired drawing from memory and the clinical form and severity of aphasia, left brain-damaged patients received a standard test for the examination of aphasia currently used in our clinic. Patients defined as aphasic were divided into 4 major aphasic syndromes (Broca's, Wernicke's, anomia and conduction aphasia) according to the following behavioural criteria.

> *Broca's aphasia*: reduced speech flow, with articulatory disorders and agrammatism or disprosody; comprehension good or moderately impaired.
>
> *Wernicke's aphasia*: normal of logorrhoeic speech flow, with phonemic and verbal-semantic paraphasias, neologisms and moderate to severe disorders of language comprehension.
>
> *Anomia*: appreciable difficulties in word finding, without articulatory disorders and with few phonemic or verbal-semantic paraphasias; comprehension good or mildly impaired.
>
> *Conduction aphasia*: fluent speech without articulatory disorders but with impaired repetition and frequent phonemic paraphasias; comprehension good to mildly impaired.

The *quantity of communication* possible in oral expression and in auditory comprehension was taken as an index of the severity of aphasia. Language disorder was rated as *mild* when patients showed only a slight anomia, rare phonemic or verbal-semantic paraphasias or a mild syndrome of phonetic disintegration, without obvious comprehension disorders. Aphasia was rated as *moderate* when anomia, phonemic or verbal paraphasias and articulatory disorders were more evident and when clear disturbances were also observed at the receptive level. The aphasic syndrome was rated as *severe* when verbal comprehension was poor and expressive language was limited to incomprehensible jargon or to few recurring utterances.

Impairment at the semantic-lexical level of integration of language. The presence of semantic-lexical impairment was studied by administering to all the aphasic patients the Verbal Sound and Meaning Discrimination test (Gainotti *et al.*, 1975). It is sometimes difficult to assess the presence of a semantic-lexical disorder at the expressive level, since other expressive disturbances can mask the semantic disorder and render its detection difficult. On the other hand, semantic impairment can be detected more readily at the receptive level by asking patients to discriminate the meaning of a given word by choosing from an array of semantically similar alternatives the object corresponding to the stimulus word. The Verbal Sound and Meaning Discrimination test has already shown itself to be particularly useful from this aspect (Gainotti *et al.*, 1975; Gainotti and Lemmo, 1976; Gainotti *et al.*, 1979) and was therefore also employed in this study. Patients with more than 3 *semantic discrimination errors* on the Verbal Sound and Meaning Discrimination test were considered to be impaired at the semantic level (3 was the worst score attained by more than 95 per cent of normal controls), whereas patients with less than 3 semantic discrimination errors were considered as free from semantic-lexical impairment.

TABLE 1 AGE, SEX, EDUCATION AND AETIOLOGY OF THE SUBJECT GROUPS

Subject group	*Mean age (yrs)*	*Sex*		*Years of schooling*	*Aetiology*	
		M	*F*		*Vascular*	*Neoplastic + others*
Normal controls (n = 23)	52.45 (SD = 12.8)	13	10	8.95 (SD = 4.8)		
R. brain damage (n = 67)	59.92 (SD = 13.1)	36	31	8.35 (SD = 4.87)	41	26
Nonaphasic L. brain damage (n = 44)	50.42 (SD = 14.3)	23	21	8.51 (SD = 4.3)	30	14
Aphasics (n = 57)	57.23 (SD = 13.8)	36	21	9.37 (SD = 4.9)	38	19
Broca (n = 16)	54.64	9	7	7.55	11	5
Conduction (n = 7)	64.16	5	2	11.43	6	1
Wernicke (n = 24)	59.50	16	8	9.11	15	9
Anomics (n = 10)	51.44	6	4	8.25	6	4

In addition to the semantic distractors, this test also includes phonological and irrelevant distractors so that, besides the semantic discrimination errors, it is also possible to assess phoneme discrimination errors and unrelated errors (Gainotti *et al.*, 1975). No account was taken of these errors in the present study since our aim specifically consisted of assessing semantic-lexical impairment and only semantic discrimination errors were considered as relevant.

Subjects

The Drawing from Memory test and the Copying Drawings test were given to 57 aphasics, 67 patients with right hemisphere lesions and 44 nonaphasic left brain-damaged patients. Furthermore, 23 normal controls, showing no signs of CNS impairment, also received both tests. Brain-damaged patients were unselected. However, left-handed subjects, patients with clinical signs (or case histories) pointing to diffuse or obviously bilateral brain damage and subjects unable to carry out the drawing tasks (owing to paralysis of the right hand) were excluded. Table 1 gives the relevant clinical data (age, sex, education and aetiology of illness). No significant differences were found either between aphasic patients and any of the control groups or between the different aphasic syndromes, with respect to age, sex, education and aetiology of the brain pathology.

RESULTS

Scores Obtained by Aphasic and Nonaphasic Patients on the Tasks of Drawing from Memory and Copying Drawings

Table 2 gives the mean scores obtained by aphasics, normal controls, and nonaphasic right and left brain-damaged patients on the Drawing from Memory test and on the Copying Drawings test. A two-way analysis of variance for repeated measures, with an unequal number of observations within the various cells, gave a significant F value for both the main effects (type of task and diagnostic group) and the interaction. Separate post-hoc comparisons between the aphasics and the other diagnostic groups showed that aphasics are significantly more impaired than any other group on the Drawing Objects from Memory test, but not on the test for constructional apraxia. In particular, no difference was found between aphasics and right brain-damaged patients (which can be considered as the most appropriate control group) on the Copying Drawings test. This finding strongly suggests that impaired drawing from memory in aphasic patients is a symptom independent from constructional apraxia and cannot be considered as a particular aspect of a more general visuoconstructive disorder.

TABLE 2. RESULTS OBTAINED BY APHASICS, NORMAL CONTROLS AND NONAPHASIC BRAIN-DAMAGED PATIENTS ON THE TASKS OF DRAWING OBJECTS FROM MEMORY AND OF COPYING GEOMETRICAL DRAWINGS

	Aphasic patients $(n = 57)$	*R. brain-damaged* $(n = 67)$	*Nonaphasic L. brain-damaged* $(n = 44)$	*Normal controls* $(n = 23)$
Mean scores				
Drawing from Memory	21.59	28.08	31.16	33.78
Copying Drawings	33.83	33.53	37.70	37.04

Overall analysis of variance

Variable	df	F	*P*
Type of task	1	111.56	< 0.001
Diagnostic group	3	30.90	< 0.001
Interaction	3	5.78	< 0.01

Separate comparisons between aphasics and other diagnostic groups

Drawing Objects from Memory		
Aphasics *vs* R. brain-damaged	$t = 4.012$	$P < 0.001$
Aphasics *vs* nonaphasic L. brain-damaged	$t = 6.326$	$P < 0.001$
Aphasics *vs* normal controls	$t = 6.315$	$P < 0.001$
Copying Geometrical Drawings		
Aphasics *vs* R. brain-damaged	$t = 0.258$	P n.s.
Aphasics *vs* nonaphasic L. brain-damaged	$t = 4.057$	$P < 0.001$
Aphasics *vs* normal controls	$t = 2.016$	$P < 0.05$

In order to study the problem more closely, scores obtained on the Drawing from Memory test were submitted to an analysis of covariance using age, educational level and copying drawings scores as covariates. Adjusted mean scores for aphasics, normal controls and nonaphasic right and left brain-damaged patients on the Drawing from Memory test are given in Table 3, together with the results of the overall analysis of variance and with the post-hoc comparisons between aphasics and other diagnostic groups. Results of this analysis confirm that defects in drawing from memory in aphasic patients are independent from visuoconstructive disorders, since they are still evident when variance associated with constructional apraxia has been removed from analysis.

TABLE 3 ADJUSTED MEAN SCORES FOR APHASICS, NORMAL CONTROLS AND NONAPHASIC BRAIN-DAMAGED PATIENTS ON THE DRAWING FROM MEMORY TASKS

Adjusted mean scores

Aphasics	*R. brain-damaged*	*Nonaphasic L. brain-damaged*	*Controls*
20.81	27.34	27.00	30.49

Statistical analysis

Analysis of covariance $F_{(1\ 151)} = 16.89$ $P < 0.001$

Post-hoc comparisons between aphasics and other groups by the 'Tukey test' (t crit. 0.001 = 4.08)

Differences between mean scores	Aphasics—R. brain-damaged	= 6.53
	Aphasics—nonaphasic L. brain-damaged	= 6.19
	Aphasics—controls	= 9.68

Relationship between Impaired Drawing from Memory and Clinical Aspects of Aphasia

When a more detailed study of the relationship between impaired drawing from memory and clinical aspects of aphasia was undertaken, it was found that neither the clinical type nor the severity of aphasia are significantly related to the inability to reproduce from memory the form of real objects. In fact, no significant difference was found between the drawing from memory scores obtained by Broca, Wernicke, anomic and conduction aphasic patients nor among the scores obtained by patients with a mild, moderate or severe form of aphasia. Table 4 gives the mean values for the scores obtained on the Drawing from Memory test and on the Copying Drawings test by patients classed in the various aphasic syndromes or rated as showing different levels of severity of aphasia.

Since no significant difference was found between the various aphasic syndromes or between the various levels of severity of aphasia, neither of these variables seems critical to the deficit in drawing from memory of aphasic patients. On the contrary, a significant relationship was found between impaired drawing from memory and breakdown at the semantic-lexical level of integration of language, as shown in

TABLE 4. RELATIONSHIPS BETWEEN CLINICAL FORM AND SEVERITY OF APHASIA AND RESULTS OBTAINED ON THE TASKS OF DRAWING OBJECTS FROM MEMORY AND OF COPYING DRAWINGS

	Clinical form of aphasia: mean scores			
	Broca (*n* = *16*)	*Anomia* (*n* = *10*)	*Wernicke* (*n* = *24*)	*Conduction* (*n* = *7*)
Copying Drawings	34.52	34.23	34.71	33.03
Drawing from Memory	18.74	23.32	21.78	23.10

	Mean scores obtained by patients showing various levels of severity of aphasia		
	Mild (*n* = *23*)	*Moderate* (*n* = *23*)	*Severe* (*n* = *11*)
Copying Drawings	34,78	33.60	33.55
Drawing from Memory	23.78	18.48	21.60

TABLE 5. RELATIONSHIPS BETWEEN SEMANTIC-LEXICAL IMPAIRMENT AND SCORES OBTAINED ON THE TASKS OF COPYING DRAWINGS AND OF DRAWING FROM MEMORY

Mean scores obtained by aphasic patients with and without semantic-lexical impairment

	Presence of semantic-lexical impairment (*n* = *30*)	*Absence of semantic-lexical impairment* (*n* = *27*)
Copying Drawings	33.54	35.62
Drawing from Memory	17.52	26.33

Overall analysis of variance

Variable	df	F	*P*
Type of task	1	101.38	< 0.001
Presence/absence semantic-lexical impairment	1	18.72	< 0.001
Interaction	1	3.57	< 0.05

Table 5. Patients who had made a 'normal' number of semantic errors on the Verbal Sound and Meaning Discrimination test scored significantly better on the Drawing from Memory test than patients presenting a semantic-lexical impairment ($t = 2.38$; $P < 0.05$). No difference was found between the two groups of aphasics when scores obtained on the Copying Drawings test were taken into account.

DISCUSSION

The main results of the present investigation can be summarized as follows. (1) Aphasic patients are significantly more impaired than right and nonaphasic left brain-damaged patients on a test of drawing objects from memory. (2) This impairment cannot be considered as an aspect of a more general visuoconstructive disturbance, since it remains significant even when variance associated with constructional apraxia has been removed. (3) No correlation can be found between impaired drawing from memory and the severity or clinical form of aphasia. On the contrary, a significant relationship can be observed between impaired drawing from memory and breakdown at the semantic-lexical level of language integration.

Since our study did not include a condition in which subjects were asked to draw 'nonsense' drawings from memory, we cannot exclude that poor results obtained by aphasic patients were due to a short-term visual memory defect and not to a conceptual inability to reproduce from memory the form of objects having a characteristic shape. Several reasons, however, make this interpretation rather implausible. (1) This interpretation is not economical, since it assumes that aphasic patients may also have an independent short-term visual memory defect. (2) The examiner did not ask the patient to reproduce from memory a more or less meaningful shape, but tried to raise in the patient the concept of the object (for example, by naming it) and then asked the patient to draw the named object. (3) It has been demonstrated by Faglioni and Spinnler (1969) that right brain-damaged patients, and not aphasics, are particularly impaired in tasks of immediate and delayed memory of meaningless visual patterns.

All these reasons support Bay's statement, that aphasic patients are unable, because of a basic conceptual disorder, to reproduce from memory those essential details which are necessary for a clear identification of an object (Bay, 1962, 1964, 1974) rather than a short-term visual memory defect hypothesis. Some of the present results (for example, the relationship between drawing from memory impairment and breakdown of the semantic-lexical system) seem to show that the hypothesis advanced by Bay could perhaps be formulated in more precise terms by admitting the existence, within the aphasic patients, of a selective relationship between conceptual and semantic-lexical disintegration. This last formulation also has the advantage of being compatible with the existence of aphasic individuals who have demonstrated excellent capabilities in drawing objects from memory, since it is possible that language disturbances in these subjects were due more to phonological and/or phonetic disorders than to a central semantic-lexical impairment.

Results pointing in this direction have recently been obtained by Gainotti and Lemmo (1976), Whitehouse *et al.* (1978), Gainotti *et al.* (1979) and Caramazza *et al.* (1982). Gainotti and Lemmo (1976) have shown that aphasic patients are specifically impaired on a nonverbal test of symbolic gesture interpretation and that, within the aphasic group, the inability to understand the meaning of symbolic gestures is highly related to semantic-lexical disturbances. Similar findings have been obtained by Gainotti *et al.* (1979) with a nonverbal test of 'conceptual thinking'. Aphasic patients were selectively unable to appreciate the relationship existing between the picture of a simple object and pictures of other objects having different levels of conceptual similarity with the stimulus. Furthermore, an important correlation was found, within the aphasic patients, between semantic-lexical deficits and conceptual impairment.

Also very relevant to the problem of the relationship between conceptual and semantic-lexical disintegration are the results obtained by Whitehouse *et al.* (1978) and by Caramazza *et al.* (1982), using a model of conceptual representation recently developed by Labov (1973) and by Miller and Johnson-Laird (1976). These authors administered to a group of anomic and to a group of Broca's aphasic patients a series of line drawings of food containers, varying in physical features (such as the diameter-to-height ratio and the presence or absence of a handle) and presented in a variety of contextual situations (a coffee pot, a cereal box and a pitcher of iced water). Their aim was to explore the interaction of perceptual and functional information in the act of selecting the most appropriate name for the depicted object from a multiple choice list including 'cup', 'bowl' and 'glass'. Normal controls and Broca's aphasic patients were able to integrate in a predictable way perceptual and functional information in order to choose the proper name for each stimulus, whereas anomic patients were not influenced in their choice of the verbal label either by perceptual or functional information. In interpreting these data, Caramazza *et al.* (1982) assumed that the perceptual parsing of an object (for categorization and eventually for naming) may be guided by semantic considerations (that is, by the set of features that are represented as part of the concept of the object). The inability of anomic patients to classify the stimuli correctly might be due, from this point of view, to a conceptual-semantic disorder affecting the perceptual parsing process in its 'top-down', semantically orientated stage. A very similar interpretation could be advanced, in our opinion, to explain most of the nonverbal disturbances shown by aphasic patients with semantic-lexical impairment. In particular, a defect of the conceptual organization underlying word meaning could explain their inability to reproduce from memory the form of objects, if we assume that perceptual properties are represented as part of the concept of an object, either directly or in verbal terms.

It is possible, on the other hand, that some aspects of the semantic representation may be more impaired than others in aphasic patients with semantic-lexical disorders. Goodglass and Baker (1976) have shown, for example, that some features of meaning are very impaired in aphasic patients with comprehension disorders, whereas other features are relatively spared. Furthermore, it seems to us that the drawing from memory defect studied in the present investigation was less clearly linked to the semantic-lexical impairment than the conceptual thinking disorder investigated in a previous study (Gainotti *et al.*, 1979). A comparative assessment of the levels of impairment presented by aphasic patients on various kinds of nonverbal cognitive tasks could, therefore, be very informative in obtaining a better knowledge of this complex and debated issue.

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TIME OF CONSCIOUS INTENTION TO ACT IN RELATION TO ONSET OF CEREBRAL ACTIVITY (READINESS-POTENTIAL)

THE UNCONSCIOUS INITIATION OF A FREELY VOLUNTARY ACT

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SUMMARY

The recordable cerebral activity (readiness-potential, RP) that precedes a freely voluntary, fully endogenous motor act was directly compared with the reportable time (W) for appearance of the subjective experience of 'wanting' or intending to act. The onset of cerebral activity clearly preceded by at least several hundred milliseconds the reported time of conscious intention to act. This relationship held even for those series (with 'type II' RPs) in which subjects reported that all of the 40 self-initiated movements in the series appeared 'spontaneously' and capriciously.

Data were obtained in at least 6 different experimental sessions with each of 5 subjects. In series with type II RPs, onset of the main negative shift in each RP preceded the corresponding mean W value by an average of about 350 ms, and by a minimum of about 150 ms. In series with type I RPs, in which an experience of preplanning occurred in some of the 40 self-initiated acts, onset of RP preceded W by an average of about 800 ms (or by 500 ms, taking onset of RP at 90 per cent of its area).

Reports of W time depended upon the subject's recall of the spatial 'clock-position' of a revolving spot at the time of his initial awareness of wanting or intending to move. Two different modes of recall produced similar values. Subjects distinguished awareness of wanting to move (W) from awareness of actually moving (M). W times were consistently and substantially negative to, in advance of, mean times reported for M and also those for S, the sensation elicited by a task-related skin stimulus delivered at irregular times that were unknown to the subject.

It is concluded that cerebral initiation of a spontaneous, freely voluntary act can begin unconsciously, that is, before there is any (at least recallable) subjective awareness that a 'decision' to act has already been initiated cerebrally. This introduces certain constraints on the potentiality for conscious initiation and control of voluntary acts.

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INTRODUCTION

The 'readiness-potential' (RP), a scalp-recorded slow negative potential shift that begins up to a second or more before a self-paced act (Kornhuber and Deecke, 1965; Gilden *et al.*, 1966), can also precede self-initiated 'freely' voluntary acts which are not only fully endogenous but even spontaneously capricious in origin (Libet *et al.*, 1982). The appearance of preparatory cerebral processes at such surprisingly long times before a freely voluntary act raises the question of whether conscious awareness of the voluntary urge or intention to act also appears with such similar advance timings. The present study attempts to answer this question experimentally.

In the present study, the experience of the time of the first awareness of the urge to move was related by the subject to his observed 'clock-position' of a spot of light revolving in a circle; the subject subsequently recalled and reported this position of the spot. Thus the experience of timing of the awareness was converted to a reportable, visually related spatial image, analogous to reading and recalling the clock-time for any experience. (The reliability and validity of this operational criterion are further considered below.) This indicator of the time of the conscious experience could then be related (1) to the actual time of the voluntary motor act, as indicated by the electromyogram (EMG) recorded from the appropriate muscle, and (2) to the time of appearance of the simultaneously recorded RP that is generated by the brain in advance of each act. The voluntary motor acts under study were those produced with minimal or no restrictions on the subject's independent choice of when to act, and under instructions that encouraged spontaneity of each volitional urge to act (Libet *et al.*, 1982).

The present findings thus provide experimental evidence on the timing of the conscious intention to act relative to the onset of cerebral activity preparatory to the act, and on the roles of conscious processes in the initiation of a freely voluntary motor act.

METHODS AND PROCEDURES

Subjects

Six right-handed college students were studied as two separate groups of three each. Group 1 comprised 3 females (S.S., C.M. and M.B.), but the quality of the EEGs and the minimal amplitude of the RPs of one precluded using much of her data. Group 2 consisted of 2 males and 1 female (S.B., B.D. and G.L.). Study of this group began a few months after completing the study of Group 1.

Recording

The d.c. recording and averaging of the EEG has been described (Libet *et al.*, 1982). For present purposes, analysis of RPs is made for those recorded at the vertex, where they were all maximal. (For the first 4 experimental sessions with Group 1, only the contralateral precentral recording site is available.) Linked mastoid electrodes served as the reference lead, with a ground electrode on the left ear lobe. Controls excluded the electro-oculogram as a source of the slow potentials. In each experimental series, 40 trials were performed and averaged by a computer of average transients (CAT 400B). The 2 s period of EEG stored by the CAT with each trial included a 1.4 s period already on the recording tape before 'O-time'. The latter was signified by the EMG, recorded with bipolar electrodes on the skin over the activated muscle of the right forearm.

Procedure

The subject sat in a partially reclining position on a lounge chair with an observer present in the room. Each trial was started only when the subject considered himself comfortably ready. The trial began with a brief 'get-ready' tone. This signalled that during the next 1-3 s the subject should relax his muscles, especially those of the head, neck and forearm, blink his eyelids if he wished, and fix his gaze on the centre of the 5 inch circular screen of a cathode ray oscilloscope (CRO) that was positioned at about 1.95 m away in his direct line of vision. At the end of these irregular get-ready periods the operator activated the PDP-12 computer to initiate circular revolution of the beam of the CRO. The CRO spot of light revolved in a clockwise circle near the circumference of the screen starting from the '12-o'clock' position; this motion simulated a sweep secondhand of a clock but each revolution was completed in 2.56 rather than 60 s. A circular scale, with numbers at each '5 s' position, was mounted at the external edge of the CRO screen, and a plastic grille on the peripheral portion of the screen displayed illuminated radial lines spaced at '2.5s.' intervals (each equal to 107 ms of actual time). Subjects were asked to maintain their gaze fixed on the centre of the CRO screen and not to follow the CRO spot around, even though they were to report information relating the 'clock-position' of the spot to the events (*see below*). The visual angle subtended between the centre and the peripheral position of the moving spot was small enough (1.8 deg) to present no difficulty from loss of visual acuity. The 'clock-time' of the CRO spot at each event, namely EMG with motor act or stimulator synch pulse with stimulus to skin, was recorded by the PDP-12 computer. Subjects were trained to make their self-initiated movement sufficiently brisk so that within no more than 10-20 ms from the start of any EMG potentials they achieved the amplitude pre-set to trigger the computer.

The subject was asked not to blink from the time the CRO spot started revolving until after the event. To minimize the possibility that the need to blink might become a controlling 'external' factor that compels or impels him to act, the subject was told that he may blink during the trial if the need arose; but that, if he did blink (or made some other extranaeous motion), he should then simply wait for the CRO spot to make at least another full revolution before performing the quick voluntary movement, as at the start of the trial.

Two different kinds of series were studied.

(1) *Self-initiated voluntary acts*. The subject was asked to wait for one complete revolution of the CRO spot and then, at any time thereafter when he felt like doing so, to perform the quick, abrupt flexion of the fingers and/or the wrist of his right hand (*see* Libet *et al.*, 1982). An additional instruction to encourage 'spontaneity' of the act was given routinely to subjects in Group 2 and only in the latter half to two-thirds of sessions with Group 1. For this, the subject was instructed 'to let the urge to act appear on its own at any time without any preplanning or concentration on when to act', that is, to try to be 'spontaneous' in deciding when to perform each act; this instruction was designed to elicit voluntary acts that were freely capricious in origin.

(2) *Skin-stimuli 'at unknown times'*. For such a series the subject expected to receive a near-threshold stimulus pulse on the back of the right hand. Delivery of the pulse was made by the operator at irregular times that were unknown to the subject, but only after the CRO spot completed its first revolution. They were actually delivered randomly during the second or third revolution of the spot (that is, between about 2.6 and 7.6 s after the spot began to revolve); this range overlapped with that for the times of the self-initiated movements. These conditions closely parelleled the attentive and other requirements associated with performing and recalling the CRO clock time for 'spontaneous' self-initiated voluntary acts (*see also* Libet *et al.*, 1982).

Subjects' reports of the time of an event. The 'clock position' of the revolving CRO spot at the time of the subject's awareness of an event was observed by the subject for later recall. Within a few seconds after the event, the subject was asked for his report of that timing, as in recalling a spatial image of ordinary clock time in conjunction with another event. It was emphasized that only an after-the-event recall of the experience was required, and that the subject should not worry about the task in advance of each event. Subjects became rapidly accustomed to this task during the training runs and did not find it to be taxing or stressful; nor did this task have any detectable effect on RPs (Libet *et al.*, 1982).

Modes of recall. Although each report depended on the subject having continously monitored the revolving CRO spot and visually noting, to himself, the position of the spot at the actual time of his awareness (of the event under study—*see below*), two different modes were employed for his after-the-event recall of that spot position. With the (A) or 'absolute' mode, the subject was asked to look back on the circular time scale mounted on the CRO and report the 'clock-time' of the spot position in 'seconds'. (Each 'second' on this scale corresponded to an actual time of 2560/60 or about 42.7 ms.) With the (O) or 'order' mode, the subject was asked to report the order of the final stopped position of the CRO spot, at the end of the trial, relative to his recalled position of the moving spot at the time of his awareness. For this, the subjects simply reported 'CRO spot (stop-position) first', at an earlier clock-position than the event-awareness; or 'awareness first', or 'together' (same position for both, insofar as the subject could discriminate). The (O) mode of recall was found by most subjects to be somewhat less demanding than the (A) mode.

The final stop position for the CRO spot following each event was arrived at in a complex manner that differed for (A) or (O) mode of recall. When either of the modes of recall was to be used, the computer continued the clockwise motion of the spot for a period beyond the time triggered by the event; this was called the 'contination interval'. The continuation interval could have one of 20 different values, all in the range between +500 and +800 ms (approximately 12 to 19 'seconds' of clock-dial). One of these continuation values was selected by the computer, from a randomized series of the 20, for use in a given trial. No violations of independence of answer were found in relation to the randomized continuation intervals.

For the (O)-order-mode only, however, the CRO spot did not stop after reaching its continuation interval; instead the spot jumped discontinuously, to stop at clock positions that were both before and after the subject's recalled positions for his awareness. (1) 'Stopping range'. The clock-times within which all of these final stop positions were included (the 'stopping range') ordinarily spanned 600 ms of real time. The positive and negative end points of the stopping range, relative to zero trigger time for each event (EMG or S-synch pulse), were chosen so as to span the entire range of times (relative to O) in the reports for a given awareness (W, M or S, *defined below*). We usually succeeded in setting the positive end of the stopping range well beyond the stop-times of the CRO spot for which all reports were 'W-first' (or M- or S-first), that is, earlier than the stopped spot position; and the negative end of the stopping range well beyond the stop-times for which all reports were 'spot first' (as in fig. 1B). Actual distributions varied with the subject. The beginning and end points of the 'stopping range' were therefore set individually before each series of trials, depending on previous results with the kind of awareness to be reported and with that subject (*see* examples in fig. 1); the training series of 10 trials that routinely preceded each regular series of 40 trials was useful for this purpose. (2) 'Stop-times'. Within each selected stopping range that spanned 600 ms, one of 40 different actual stopping times for the CRO spot, at intervals of 15 ms, was randomly selected by the computer for use after each of the 40 events. A different sequence of these randomized stop times could be preselected for the successive 40 trials in given series, so that a given sequence of stop-times was not repeated in a given session. The length of the 'continuation-interval', that precedes the final jump of the spot to its stop-time (*see above*), was randomly varied in a fashion that was independent of the randomized sequences selected for the final stop-times. The objective of all this was of course to avoid providing any clues that might relate the stop-time position of the CRO spot to the clock-time of the event itself.

The O procedure would not seem to be subject to the kind of artefactual difficulty described by Garner (1954). In the latter's case, subjects were asked to judge 'half-loudness' referred to a standard acoustic stimulus; each subject gave reliably consistent judgements, but these turned out to be appropriate only with reference to each different range of stimulus intensities presented rather than to the standard stimulus. In our case, the stopping range of reference times was determined for each subject from his own range of reported W times, as indicated by initial trials, rather than *vice versa.*

There were some series for which the adopted stopping range did not appropriately span the full range of potential reports by the subject; that is, the numbers of 'W first' and 'spot first' reports were far from equal, with few or no reports for one of these possible responses. This indicates that the subject was not shaping his reports to correspond to the adopted range of stop-times for the CRO spot. In such instances, the series had to be repeated, in the same or a later session, with a more suitable stopping range that could result in a statistically usable analysis for the mean W time in the series. Additionally, the subject had no prior knowledge of or consistent experience with the actual stopping ranges that were used. In a usual given experimental session, each separate series for W, M and S awareness times required a different stopping range. This meant that the subject did not have any consistent stopping range with which he was repeatedly presented in successive series.

Type of 'awareness' to be timed by the subject. Three different subjective experiences were to be timed. Each series of 40 trials involved reports of only one of these for all 40 events.

(W). In W series, the subject was asked to note and later report the time of appearance of his conscious *awareness of 'wanting' to perform* a given self-initiated movement. The experience was also described as an 'urge' or 'intention' or 'decision' to move, though subjects usually settled for the words 'wanting' or 'urge'. Subjects were told there were no right or wrong or inaccurate answers possible in the W and M series; that we simply wanted their best recollection and report of their own experience. Subjects were also asked, after completing a series of 40 self-initiated acts, whether any of the acts occurred without their experiencing any prior awareness of an urge or intention to act, that is, whether they were 'surprised' to realize a voluntary act had occurred without a conscious prior intention. In three series, subjects (3 of the 5 studied) did report that some, usually a small number, of the 40 acts 'surprised' them (Libet *et al.*, 1982), although the mean W time for such series of 40 was negative to EMG zero time, as usual. Asking subjects about 'surprise' acts should have indicated to them that it was acceptable even to have and to report the absence of a conscious urge or intention to act prior to a self-initiated act. The fact that instances of 'surprises' were reported increases confidence that the reports of timing prior to the act represented endogenous experiences not defined or induced by the instructions.

It was emphasized that the reported time should refer to the earliest appearance of the W awareness that might precede an actual movement; the subjects easily distinguished this specific urge to act from any awareness of a more general preplanning nature that might precede W, as in association with type I RPs (*see* Libet *et al.*, 1982), and also from an occasional urge to move that was not followed by an actual movement.

(M). In M series, the time of subject's *awareness* that he/she '*actually moved*', in the self-initiated act, was to be noted and reported after each trial. This was intended to provide an instruction for timing an experience related to but different from that of W, and thus to act as a partial test of the validity of the W timings. Some subjects stated, on their own, that their mental set differed somewhat in W *vs* M series. In a W series there was a feeling of active attention to or 'watching for' the awareness of wanting to move, so as to be able to note the time of its appearance, although the urge to move arose spontaneously with no preplanning; but M series proceeded without such advance 'watching' for the event to occur. It should be emphasized that any such difference in mental set did not appear to affect the associated RPs, which had similar forms and onset times for W and M series (*see* Results, *below*).

(S). In S series, time of *awareness of the sensation* elicited by the near-threshold stimulus pulse to the back of the hand, delivered at randomly irregular times unknown to the subject, was to be noted and reported after each trial. The attentive and other conditions of this task closely paralleled those for the W and M series, except that the event was an externally-induced sensory instead of a self-initiated motor one. After each S series, whether for training or experimental purposes, the subject was given a rough indication of how close he was to the actual times for the stimuli, as an aid in improving accuracy in all the experiments. If the awareness times reported in an S series were to differ significantly from the actual times of the stimulus pulse in each respective trial, the mean difference between the reported and actual stimulus times may be regarded as a measure of that subject's 'bias', when observing and reporting awareness times under the experimental conditions employed (*see* Libet *et al.*, 1979). This would include errors in making simultaneous judgements of the times for a mental event (sensation here) and a visual event (position of the CRO spot) (*see* Discussion). There were in fact mean differences or 'shifts' for S that were characteristic for each subject.

Progression of the experiments. The first (and, in some cases, the second) half-day session was purely for training purposes. Subsequently, each subject was studied in 6 to 8 regular half-day sessions, usually 1 per week. Each of the first 4 regular sessions began with a training series of 25 trials with skin stimuli intended as a retraining of reporting the recalled times of a subjective experience. This series differed from the experimental S series (of 40 trials) in that, after each 5 trials of this series, the subject was told what the actual 'clock-times' were for the skin stimuli, whose randomly irregular delivery times were not known before the trials. Following this there were two 40-trial series of self-initiated acts, one W and one M, each preceded by a briefer 10-trial series for retraining purposes, and then one 40-trial series of skin stimuli delivered at unknown times (S). The order of W and M series within a session was alternated for each successive session. A given mode for subjects to recall clock-positions of the revolving spot, (A) *vs* (O), was used for all series in a given session, but the modes were alternated for successive sessions. In sessions after the first 4, few M or S series were studied.

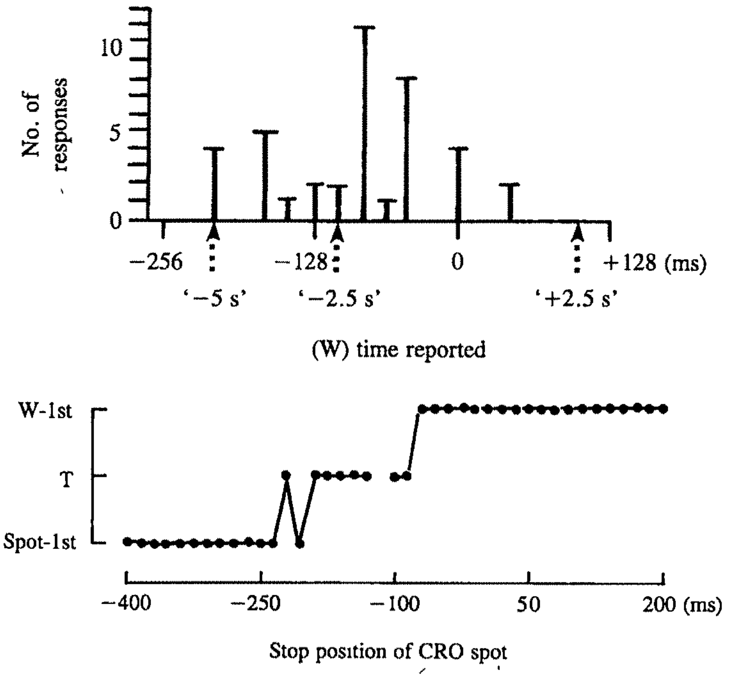

FIG. 1. Examples of plots of a subject's reports of (W) time after each trial in series of 40 self-initiated, voluntary movements. A, series in session 3 for subject S.B. mode of recall is 'absolute' (A); i.e. subject reported 'clock-time' of CRO spot at time of first awareness of 'wanting' to move. From this value, the 'clock-time' of the EMG-trigger was subtracted; the resultant net (W) time, relative to EMG zero time, was plotted Abscissa indicates both the net 'clock-time' in seconds on the dial (arrows) and the corresponding net real times for (W). B, series in session 2 for subject S.B. mode of recall is by 'order' (O). The subject reported one of three alternatives for his recalled position of the revolving spot at the initial awareness of W. As indicated on the ordinate these were 'W-first' (W time earlier than the final stop-position of the CRO spot); or 'Spot-first'; or 'together', T (W time indistinguishable from or same as for the final stop-position of the spot). The 'stopping range', within which lay all the 40 different stop-positions of the spot, randomly sequenced in the series of 40 trials, was set between 200 ms positive to (i e., later than) and 400 ms negative to the EMG zero time in each trial. (Since both ends of the 600 ms stopping range were included, the computer actually designated 41 stop-positions at 15 ms intervals, but the subject did not report W time for the 41st trial of the series. This accounts for an absence of a report at the stop-time of −115 ms in the figure, which happened to be the randomly sequenced stop-time of the CRO-spot in the 41st trial of this series.)

Statistical handling of the response times. This is described in relation to the data in two actual series, one in (A) and one in (O) mode of recall (plotted in fig. 1). For each event in a series of 40 with (A) mode of recall, the 'clock-time' in 'seconds' for EMG-trigger time is subtracted from the 'clock-time' of the CRO spot at the time of awareness, as reported by the subject; this gives a net reported clock-time (relative to 'EMG zero time'). Each net reported clock-time is then converted to real time, and these W times (reported real time of each awareness of wanting to move, relative to EMG zero time) are plotted for that series. (Each 60 s of 'clock-time' = 2560 ms actual time.) For example, in fig. 1A we see that subject S.B. reported W times of 43 ms twice, O ms 4 times, −43 ms 8 times, etc. (as converted from net reported clock-times of 1, 0, −1 'seconds', respectively). Averaging these values for the whole series gives a mean shift for W, relative to EMG-O time, of −2.1 'seconds' of clock-time or −90 ms of real time.

For the (O) mode of recall we have extended to trinomial data the idea presented by Church and Cobb (1971). With this technique, the mean W shift was calculated as:

(upper, positive end of 'stopping range') − (time interval between 'stop times') × (number of points − 1/2)

'Stopping range' and 'stop-times' are defined above. 'Number of points' is calculated by giving 1 point for each time the subject says 'W first' (i.e. spot position at time of awareness has an earlier 'clock-time' than the final 'stop-time' of the CRO spot), and 1/2 point for each response of 'together' (i.e. W time and stop-time of spot appear the same to the subject). (In some series a trial was 'aborted' or a subject's report was not available, for some technical reason. In such a case that trial was considered to contribute a number of points equal to our estimate of the probability that the subject would say 'W first' for that particular 'stop-time' of the CRO spot.) In the example shown in fig. 1B, the responses for each of the different 'stop-times' are plotted. In that series, the upper end of the 'stopping range' was 200 ms after EMG-trigger time (lower end was −400 ms), with the usual minimum 15 ms time interval between stop-times within the 'stopping range' of 600 ms. There were 19 'W first' responses and 8 'Together' responses; the remaining responses were of course 'Spot first'. There was one trial with a missing report in this series, at the CRO stop-time of −115 ms; we estimate the probability of saying 'W first' as 1/2 in this case. Putting this together, our estimate of the mean shift for W is

$$200-15\,(19+8/2+1/2-1/2) = -145 \text{ ms}$$

The mean shifts for the awareness in an M or S series were computed in an analogous manner for A or O mode of recall, respectively, using the stimulator-synch trigger for zero time in the S series.

RESULTS

I. Subjective Timings

The mean values of the 40 reported times of awareness (whether for W, M or S), for each series in a given study session, are presented in Table 1, A. Each value is for net time relative to 'zero-time' for each event, that is, W or M relative to EMG zero time for activation of muscle in a self-initiated movement, or S relative to stimulus-pulse time in the case of skin stimuli delivered at irregular times. There were no obvious or consistent differences between sessions in which mode of recall of time was 'absolute' (A) or by order (O) relative to final 'clock-position' of the spot (*see* Methods).

The mean value of W in each series, that is of the recalled times for being aware of 'wanting' to move, was invariably in advance of or negative to the EMG zero time. The average of all such mean Ws was about −200 ms (Table 2D). Except for the nature of the event, the basic procedures for attentive monitoring of the revolving spot and of noting visually and later recalling the clock-position of the spot, in connection with appearance of an awareness, were the same for M ('actually moved') or for S (skin sensation produced by irregularly timed, stimulus pulse) as they were for W. Reported times for S might be expected on the average to be close

TABLE 1

Column A. Awareness times (W) and, column B, RP-onset times, for each 'W series' of 40 self-initiated movements. Awareness times also given for (M) and (S) series in same session. RP onsets are given for both the 'main negative shift' (MN) and for time at which 90 per cent of total area under the RP begins (*see* text for definitions of W, M and S). Column C. *Differences* (ms) between RP onset-times and W times ('uncorrected', and 'corrected' for S), taking RP onset either for the main negative (MN) component or for 90 per cent of the RP area, in each W series of 40 self-initiated acts. (Instances in each series of 40 trials when the W time preceded [was negative to] onset of RP are given after RP_{MN} onset for the respective series.)

			A *Awareness times (ms)*						B *Onset of RP (W series)*			C. *(Onset RP) minus (W), i e* (B)-(A), *using*			*(Onset RP) minus (W-S), using*	
		Mode	*(W)*		*(M)*		*(S)*									
Subject	*Session*	*re-call*	$\bar{x}$	*SE*†	$\bar{x}$	*SE*	$\bar{x}$	*SE*	*Type RP**	*Onset 'MN'*	*Onset 90 % area*	RP_{MN}	*Ws neg to MN*	$RP_{90\%}$	RP_{MN}	$RP_{90\%}$
S B	1	A	− 54	11	− 21	15	− 12	11	II	− 550	−1076	− 496	0	−1022	− 508	−1034
	2	O	−145	19	− 48	20	− 53	15	II	− 900	− 729	− 755	0	− 584	− 808	− 637
	3	A	− 90	11	− 72	12	− 42	12	I	−1100	− 863	−1010	0	− 773	−1052	− 815
	4	O	−188	34	− 95	20	− 53	18	I	−1150	− 757	− 977	0	− 584	−1030	− 637
	5a	A	−123	16					II	− 800	− 876	− 677	0	− 753		
	b	A	−119	10					I	− 950	− 694	− 831	0	− 575		
	6a	A	−118	13			+157		I	− 900	− 685	− 782	0	− 567	− 625	− 410
	b	A	−161	15					II	− 600	− 484	− 439	0	− 323	− 282	− 166
G.L	1	O	−208	28	−213	28	−147	28	II	− 500	− 380	− 292	0	− 172	− 439	− 319
	2	A	−422	24	−172	22	−184	30	I	−1200	− 755	− 778	0	− 333	− 962	− 517
	3	O	−377	27	−220	26	−217	30	I	− 900	− 635	− 523	0	− 258	− 740	− 475
	4	A	−258	21	−201	25	−120	25	II	− 800	− 593	− 542	0	− 335	− 662	− 455
	5a	O	−213	42					I	− 900	− 599	− 687	0	− 386		
	b	O	−283	34					I	−1200	− 866	− 917	0	− 603		
	6a	O	−221	34			−164	20	II	− 600	− 563	− 379	0	− 342	− 543	− 506
	b	O	−271	40					I	−1400	− 765	−1129	0	− 494	−1293	− 658
B D	1	A	−225	19	+ 92	10	+135	13	II	− 400	− 295	− 175	3	− 70	− 40	+ 65
	2	O	−145	24	− 3	25	+ 45	26	III	− 225	− 157	− 80	1	− 12	− 35	+ 33
	3	A	−152	14	+ 76	12	+ 61	9	II	− 500	− 401	− 348	0	− 249	− 287	− 188
	4	O	−142	18	+ 40	21	+ 90	20	II	− 425	− 469	− 283	0	− 327	− 195	− 239
	5a	O	−145	29					III	− 250	− 716	− 105	0	− 571		
	b	O	−108	46					III	− 325	− 210	− 217	1	− 102		
	6a	O	−146	30					II	− 650	− 468	− 504	0	− 322		
S S	1	O	−235	31	−168	25	−130	27	III_c	− 250	− 806	− 15	3	− 571	− 145	− 691
	2	O	−253	28	− 33	19	− 83	17	II_c	− 400	− 282	− 147	0	− 31	− 230	− 112
	3	O	−255	26	−153	24	− 75	24	II_c	− 400	− 281	− 145	2	− 26	− 220	− 102
	4	A	−283	19	−113	9	−157	13	III_c	− 300	− 695	− 17	17	− 412	− 174	− 569
	7a	A	−248	20					I_v	− 900	− 915	− 652	0	− 667		
	b	A	−236	17					II_c	− 400	− 604	− 164	4	− 368		
	c	A	−209	16					I_v	−1100	− 805	− 891	0	− 596		
C M	1 (30 trials)	O	−287		−138		− 63		II_c	− 500	− 408	− 213		− 121	− 274	− 184
	2	O	−223	25	−123	21	− 23	20	II_c	− 400	− 489	− 177	0	− 266	− 200	− 289
	3	O	−245	25	− 83	20	− 23	27	(no RP available)							
	4	A	−132	17	− 69	10	+ 29	10	II_c	− 600	− 520	− 468	0	− 388	− 439	− 359
	6	A	−211	13					II_v	− 400	− 781	− 181	1	− 570		
									II_c	− 400	− 227	− 181	1	− 16		
	7a	A	−260	17					I_v	−1000	− 703	− 740	0	− 443		
									I_c	−1050	− 694	− 790	0	− 434		
	b	A	−251	17					II_c	− 450	− 368	− 199	2	− 117		
	8	A	−204	16					II_c	− 475	− 479	− 271	1	− 275		

* All values for subjects S B, G L and B D are for RPs recorded at the vertex For subjects S S and C.M the relevant RPs were recorded only at the contralateral precentral area for the hand, as designated by subscript c, except for some vertex recordings noted by subscript v Simultaneous values for v and c are given for sessions 6 and 7a of subject C.M † SE = standard error for our estimate of the mean value

to zero (actual stimulus time) or possibly delayed slightly. But the actual mean values for S were usually negative rather than positive or delayed, except for subject B.D., and they differed for each subject and with each session. The value obtained for S in a given session could be regarded as at least a partial measure of the way the subject is handling those reporting factors that S and W series do have in common. As an approximation, one may 'correct' W for the subject's 'bias' in reporting awareness time by our methods, by subtracting S from W for that given session. The average of all W values (about −200 ms) would be changed to about −150 ms by subtracting the average of about −50 ms for all S values (*see* Table 2D).

TABLE 2. *GRAND AVERAGES* (MS) FOR ALL SERIES IN EACH COLUMN OF TABLE 1, ACCORDING TO TYPE OF ASSOCIATED RP AND TO ORDER OF W AND M SERIES IN A SESSION

Type of RP, for W series		A. *Awareness times*	B. *Onset of RP (in W series)*		C. *B-A; i.e., (Onset RP) minus (W), using*			*(Onset RP) minus (W-S), using*	
	n	*W*	RP_{MN}	$RP_{90\%}$	RP_{MN}	$RP_{90\%}$	*n*	RP_{MN}	$RP_{90\%}$
I	12	−233	−1025	−784	−825	−522	6	−950	−585
II	20	−192	−535	−527	−343	−333	14	−366	−323
III	5	−183	−270	−517	−87	−334	3	−118	−409

D. *Awareness times*

	W		*M*		*S*	
	n	$\bar{X}$	*n*	$\bar{X}$	*n*	$\bar{X}$
For all series	37	−204	20	−86	22	−47
In sessions when W series done before M series	10	−191	10	−92	10	−41
In sessions when M series done before W series	10	−240	10	−80	10	−53

Mean values for M series were also mostly negative (except for subject B.D.), averaging about −85 ms for all mean Ms (Table 2D). M was also slightly negative to S in almost every individual study session (*see* Table 1, column A); so that even if the average of M values (−86 ms) are 'corrected' by subtracting the average of S values (−47 ms), a small average net M of about −40 ms still remains. (Even for subject B.D., subtracting the average of his mean Ss, +83 ms, from the average of mean Ms of +51 ms in the same 4 sessions, produces a net 'corrected' average M of about −30 ms.) This produces the unexpected result that reported time of awareness of 'actually moving' generally preceded the activation of the muscle at EMG zero time! (*See* Discussion.)

It is important to note that mean W values were consistently negative to mean M values in the respective session for each subject (Table 1A), in spite of the frequently negative values for M. The average of all mean Ws (about −200 ms) indicated that awareness of wanting to move preceded average awareness of actually moving (about −85 ms) by more than 100 ms. When only those W values obtained in the same 20 sessions with M values are included, the average of mean Ws was −216 instead of −204 ms (Table 2D). Mean Ws obtained in sessions when an M series was carried out before the W series appeared to be significantly more negative than Ws obtained when a W series was carried out before an M series (*see* separate averages in Table 2D). A Wilcoxon test for this ranking order gave a one-sided $P = 0.038$, and a two-sided $P = 0.076$. (This ranking was not related to the use of (A) *vs* (O) mode of recall in the session.) However, the actual differences of about 50 ms between the two sets of Ws are relatively unimportant when comparing W times to onset times of the corresponding readiness potentials (*see* Section III, *below*).

II. Onset Times of Readiness-potentials (RP)

RPs associated with the freely voluntary, self-initiated movements employed in this study have been described (Libet *et al.*, 1982). They can be categorized into two or three types, based on their form and the time of the main negative (MN) shift (*see* Tables 1B and 2B). Type II (and III) RPs are obtained when all 40 self-initiated movements in the averaged series are reported by the subject to have originated 'spontaneously' and 'capriciously', with no recollections of preplanning experiences for any of the 40 events in the series. Additional experiences of a 'preplanning' phase are associated with type I RPs (Libet *et al.*, 1982). No significant association could be detected between mode of recall for W (that is (A) or (O)) and type of RP obtained.

Onset times of RPs listed in Table 1B are for RPs recorded in the same series of 40 self-initiated movements for which the reports of W times are given, in each respective session for each subject. This simultaneity, for RP and W observations, is important because there can be considerable variations of RP onsets in different series even in the same session (Libet *et al.*, 1982). The actual RPs for each W series listed in Table 1 for the Group 2 subjects (S.B., G.L. and B.D.) are presented in fig. 2. RPs were also obtained with each M series in the session, but onset times for these are not listed in Table 1. Onset times for RPs in M series were actually, on average, similar to those for RPs in the W series (*see also* Libet *et al.*, 1982).

Two values for onset time are given for each RP (W series) in Table 1B. (1) Onset time of the main negative (MN) shift was determined by 'eye-ball inspection', checked independently by a second investigator. (2) Onset time was also computed for the point at which 90 per cent of the area under the RP tracing preceded EMG zero time.

Onset time based on RP area was determined as follows. On an enlarged projected image, the area under the RP was measured for each interval of 50 ms, starting from EMG zero time and progressing to successive intervals in the negative (pre-EMG) direction until −600 ms; between −600 and −1400 ms, areas for 100 ms intervals were measured. Within each time interval, any areas below the baseline were subtracted from those above. In estimating total area, however, it was considered advisable to exclude any early brief shifts of potential that did not continue progressively into the main RP, as some of these

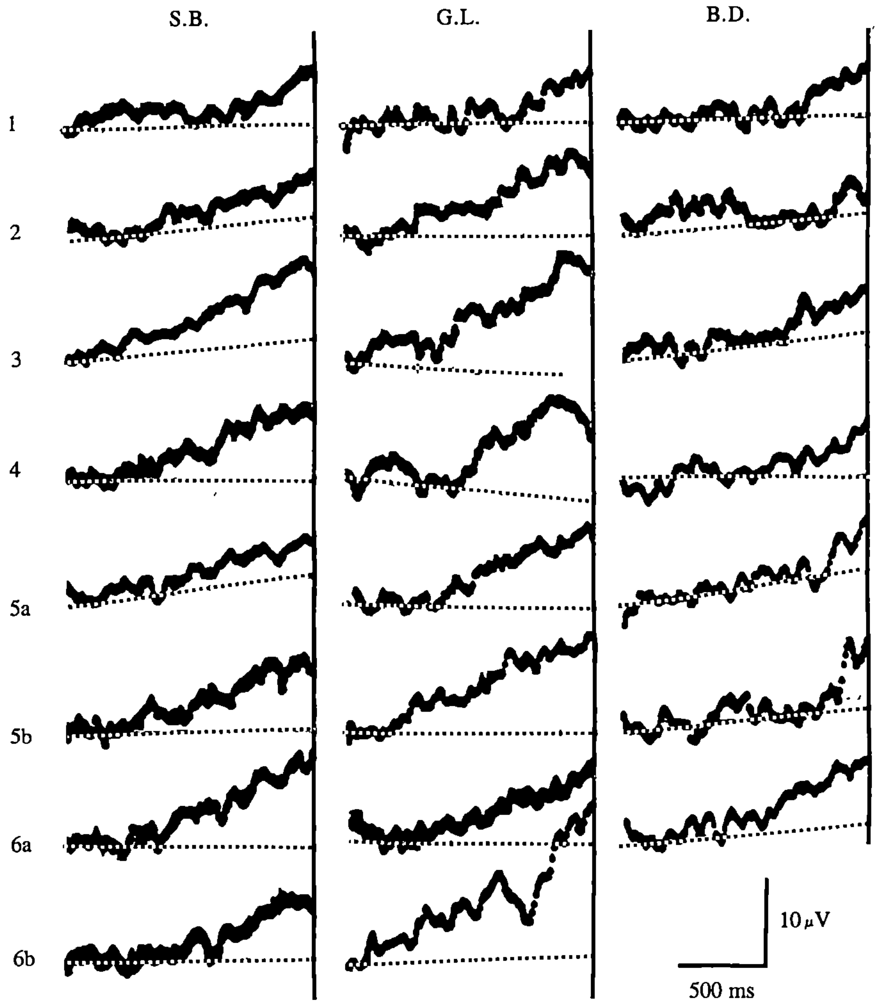

FIG. 2. Readiness-potentials (RPs) recorded at the vertex and averaged for each (W) series of 40 trials for subjects S.B., G.L. and B.D. Each RP corresponds to the respective (W) series as listed by session number in Table 1. The solid vertical line indicates the EMG zero time, marking the end of the RP. Dashed horizontal lines represent the d.c. baseline drift for the 2 s of that tracing, as estimated from the total voltage compensation for shift in d.c. level during the total time between beginning and end of that series of 40 trials.

could have been artefactual in nature. Therefore, the rule was adopted that any 200 ms segment having a total area $\leq$ 4 mm^2 (actually equivalent to 50 μV-ms) was to be regarded as zero, and that any and all areas preceding that segment were also regarded as zero. (Making the rule even more stringent, by reducing the excluding low level segment to 100 ms, rarely changed the results significantly and, when it did, the final estimates of time of onset were very little different.) It was also recognized that measurements of the beginning of the negative potential shift are subject to some possible error in judging the d.c. baseline, especially in a somewhat noisy/bumpy tracing. Therefore, after arriving at a total area for a given RP under the rule above, the time interval that included only 90 per cent of this area was computed. The 90 per cent values also fit the range of differences between the independent measurements of the areas by two different investigators.

Averages of the onset times for RP_{MN} and $RP_{90\%}$ area, respectively, for the Ws series in Table 1B are given in Table 2. The initially slower but progressive ramp-like rise of type I RPs accounts for these onset times being more negative for RP_{MN} than for $RP_{90\%}$ area. On the other hand, in types II and III RPs some definitely distinguishable negativity is often present even before the main (MN) shift. Such negativities tend to have a relatively irregular, low, amplitude but there was no reason to regard them as other than actual RP components in these self-initiated acts (*see* Libet *et al.*, 1982). Their inclusion in the measurements of total area makes it possible for onset of $RP_{90\%}$ area to precede onset of RP_{MN} in some cases. Averages of the onsets for RP_{MN} and $RP_{90\%}$ were in fact not very dissimilar for type II RPs, although individual values for the difference ($RP_{MN} - RP_{90\%}$) were in a range between -207 and $+526$ ms; but for type III RPs average $RP_{90\%}$ preceded RP_{MN} by -247 ms (range of $RP_{MN} - RP_{90\%}$ was between -115 and $+556$ ms).

III. Differences between Onset time of RP and Time of Awareness of Wanting to Move

The data comparisons given in Table 1C are central to the objective of this study; they relate the time of appearance of the *conscious* intention to act, on the one hand, to the time of onset of the *cerebral processes* before the act (as evidenced in the RP), on the other. The *difference* between RP onset time and each W awareness-time is given for each respective series of self-initiated voluntary acts. Differences are presented when utilizing the W times as actually reported (W 'uncorrected'), giving (onset RP) minus (W); or the W times 'corrected' by subtracting the reported mean time for the S obtained in the same session, giving (onset RP) minus (W-S). 'Correcting' the W value by subtracting the S value of each subject's 'bias' in reporting, did not qualitatively change the relation of RP onset-time to W; rather it generally increased the difference by which onset of RP precedes W (as 'corrected'). For subject B.D., his *positive* values for S have the oposite effect; but even for him, the only qualitatively important change in the difference is introduced in session 1, which had a large positive S (+135 ms).

It may be seen (Table 1C) that, with few exceptions, onset of RP occurred before reported awareness time by substantial amounts of time. This was true irrespective of which measure of RP-onset or of W is employed to obtain the difference. The sizes and consistency of these differences, between onset of RP and W, indicate they are highly significant. However, it is difficult to produce a rigorous quantitative value for significance of the large differences between onset of RP and W. An SD (standard deviation) for variability among individual RPs within each series of 40 is not available, as only the average RP for the whole series could be meaningfully recorded. Consequently, only the mean W value and the averaged RP obtained in a given series can be compared for statistical purposes. Confidence in the significance of the differences (in Table 1C) is further raised by the fact that they were almost invariably very large when compared to the SEs (standard errors) for the mean values of W (Table 1A). In addition, each W series of 40 trials was examined for the incidence of individual W values that may have deviated sufficiently from the mean

W so as to be negative to (precede), rather than positive to (follow) the onset of average RP in that series (*see* Table 1C). For 36 W series of 40 trials each, instances in which individual W time preceded onset time of averaged RP numbered zero in 26 series and 1 to 3 in 8 series! (Of the remaining 2 series, in both of which RPs were recorded at contralateral precentral sites where RP onsets are often less steep than at the vertex, 1 had 4 and 1 had 17 instances. The latter large value holds only in relation to onset of MN in a type III RP but not if onset $RP_{90\%}$ is used.)

The SE of each mean value for W, as given in Table 1A, is more meaningful in relation to difference of (onset of averaged RP)-(mean W), than is the SD for the distribution of the individual W values in each series of 40 trials. (The SD for each series of 40 W values may be calculated using the respective SE, given in Table 1A; $SD = \sqrt{40} \times [SE]$.) If the individual RPs were available, the difference between each RP onset and the respective individual W value could be determined for each event, and a meaningful evaluation of variability for such individual differences could be made. However, in the absence of individual RP values, it is reasonable to assume that the W and RP-onset for each individual act are probably related in a dependent and positively correlated manner, in which onset of each RP tends to be negative to (before) each W. This condition seems likely because (1) W and RP are features of the same underlying process, (2) observed differences between averaged RP and mean W were consistently large, and (3) there was a nearly complete absence of individual W values that were negative to the averaged RP (*see above*).

For reporting each W time, subjects were asked to note the earliest awareness of the specific urge or intention to act which might occur prior to the act. All subjects reported that they could distinguish readily between this awareness and any experience of 'pre-planning' that sometimes occurred in acts associated with type I RPs (Libet *et al.*, 1982). Awarenesses of 'preplanning' were completely absent in series associated with type II (or III) RPs, in which all 40 self-initiated movements were 'spontaneous' in origin. Therefore, it is useful to consider the values for type II (and III) RP series separately from those for type I RP series, as summarized in Table 2A–C. As might be expected, series with type I RPs generally exhibit an earlier onset of RP, relative to W, than do those with type II (or III), especially for RP_{MN} onsets. However, even for the series of 'spontaneous' acts with types II and III RPs, onsets of RPs generally preceded W by substantial amounts. The average of the differences [(onset RP_{MN}) minus (W)] for the 20 series with type II RPs was −343 ms (Table 2C). The relatively few sessions in which these differences were possibly not significant occurred mainly in association with type III RPs, for which onsets of RP_{MN} averaged only −270 ms. For the 5 sessions with type III RPs, the average difference (onset $RP_{MN} - W$) was −87 ms, although when $RP_{90\%}$ is used, the difference increased to −334 ms.

DISCUSSION

It is clear that neuronal processes that precede a self-initiated voluntary action, as reflected in the readiness-potential, generally begin substantially *before* the reported appearance of conscious intention to perform that specific act. This temporal difference of several hundreds of milliseconds appeared fairly consistently regardless of which of the available criteria for onset of RP or for the time of awareness are adopted. Series with type II RPs are of especial interest as all of the 40 self-initiated acts arise spontaneously; on this and other evidence, the main negative (MN) shift with average onset about −550 ms was postulated to reflect the cerebral volitional process uniquely involved in initiating a freely voluntary, fully endogenous act (Libet *et al.*, 1982). Even for such series, with type II RPs, onset of RP preceded W by about 350 ms on the average. In series with type I RPs the earlier MN shift (average onset about −1025 ms) appears to reflect a more general preparation or intention to act that can be either endogenous or cued externally; it is not necessarily associated with freedom of choosing when to act (Libet *et al.*, 1982). However, actual experiences of 'preplanning' were reported for only a minority of self-initiated acts in series with type I RPs. Consequently, the much larger differences between onset of type I RP and W, on the average as much as −800 ms, may also reflect advance cerebral preparation that is generally accomplished before conscious intentionality arises. Only in the case of a small number of series with type III RPs was the difference between RP-onset and W less negative than −100 ms, when onset of MN shift (average −270 ms) is adopted. But if start of 90 per cent of RP area (average −517 ms) rather than MN shift is taken as the criterion for onset of RP, even these type III RP's precede W by an average of more than 300 ms (Table 2C). In series with type III RPs, all self-initiated acts were also spontaneous, as in type II (Libet *et al.*, 1982).

The validity of the RP as an indicator of cerebral activity had already been established (Kornhuber and Deecke, 1965; Deecke *et al.*, 1976; Pieper *et al.*, 1980). Actually, the onset of RP provides only a minimum timing for initiation of cerebral activity, as the recorded RP probably represents neuronal activity in a limited portion of the brain, possibly that of the supplementary motor area in the mesial neocortex (Deecke and Kornhuber, 1978; Eccles, 1982; Libet *et al.*, 1982). It is possible that cerebral activity is initiated at times earlier than the onset of the recorded RP in some other regions (*see* Groll-Knapp *et al.*, 1977). For the present issue, the requirement of averaging 40 individual RPs for each recordable RP might raise the question whether this obscures an actually randomized group of widely different onset times. Even in such a case, however, there are several considerations that work mathematically against an interpretation that W times are consistently equal to or precede onset times of individual RPs. Some of these have been discussed above (Section III, Results). An example might assume that the averaged RPs are contaminated by a small number of unusual individual RPs having very early onsets, compared to onsets of most RPs in each series of 40. However, if this were true, we would expect that such unusual RPs should not appear in an appreciable number of the 40-trial series, causing the order of times for W and onset of averaged RP to be reversed; but, in fact, the onset of averaged RP preceded mean W in all of the 37 W series (Table 1C, and *see above*). Furthermore, in type II RPs the main negative shift (MN) has a relatively abrupt onset and rises rapidly; any small number of individual RPs with unusually early onsets could not appreciably affect the onset time of RP_{MN}, as measured in type II RPs. Yet, onset of RP_{MN} preceded mean W, usually by large time intervals, in all the 20 W series that exhibited type II RPs. To circumvent all these points of evidence one would have to introduce unsupported assumptions that there exist specially biased distributions of RPs.

As another possibility, it might be proposed that neural activities, represented by individual RPs with randomly variable amplitudes and onset times, must achieve some threshold, whether integrative or other, before the brain 'decides' to act voluntarily; for this one might apply a kind of 'random-walk' model for sequential decision making (*see* Audley, 1973). If applied to our case, a delayed appearance of a 'neural threshold' might coincide in time with the W time, and thus nullify any apparent discrepancy between time of cerebral decision and time of conscious intention to act. But a consistent bias or change in the random-walk distribution of the variable neural functions would have to be initiated at the onset of averaged RP, preceding the achievement of threshold for the decision. This would be analogous to the required initiation and presence of a sensory signal to produce the distribution of sensory random variables that may lead to a yes-no decision in that random-walk model (Green and Luce, 1973). Therefore, such a proposal could, at best, only separate the cerebral initiating process into two stages. An earlier stage, which would precede a final decision stage, would start with some initiating endogenous trigger. Such a model would not fundamentally affect our conclusion, that cerebral activity initiates the voluntary act before reportable conscious intention appears.

The Criteria for Time of Conscious Intention to Act

The reliability and validity of these operational criteria are of course crucial to the issue of the temporal order of cerebral processes *vs* conscious intention. The reliability of the subjects' reports of 'clock-position' for the revolving CRO spot at the time of awareness appears to be fully adequate (*see* discussion of SEs of mean W values and incidence of individual W values, relative to onset of averaged RP, in Section III of Results).

Consideration of validity of our criteria begins with the premise that the subjective event in question is only introspectively accessible to the subject himself, and that this requires a report by the subject (*see* Libet, 1965, 1966; Nagel, 1974; Creutzfeldt and Rager, 1978). Any behavioural response that is not a direct function of such a report could not be used as a *primary* indicator of the subjective event (Libet, 1981*a*, *b*), although it might be found to be associated with the subjective event as studied by suitably valid reports. Acceptance of this premise, and of our specific operational precedure for the required introspective report, introduces several issues that may affect the validity of the reported W time. In particular, factors that may affect the transmission between the subject's introspective experience and his verbal report must be considered.

(1) *Simultaneity of judgements.* Our method requires the subject to observe simultaneously, for later report, the appearance of a mental event (conscious urge to move) and the visual clock-position of the revolving spot of light at that time. Reports of simultaneous events have long been known to be subject to potential errors, depending on the circumstances (differential attentiveness, in the 'prior entry' phenomenon) and on the individual subject (*see* Boring, 1957; Efron, 1973; Sternberg and Knoll, 1973). Our S experimental series, in which subjects reported awareness times for skin stimuli, were designed to serve as controls for potential

errors in such 'simultaneity' as well as for other individual biases and errors in the entire reporting procedure. Procedures and requirements for subject's attentiveness, observations and later recall, of clock-positions of the revolving CRO spot at the time of awareness of a randomly appearing skin sensation, were the same as in the W and M series. But in the S series the actual time of the stimulus was later known to the investigator, and the error in the subject's reports could be determined objectively. The bias or error found in the S series did not qualitatively alter the difference between onset of RP and W, as determined in a given session for the same subject; in fact, they generally enlarged the differences (Table 2c).

(2) *Timing of an endogenous mental event.* The subject's reported time for spontaneously arising awareness of the urge/intention to move cannot be directly or objectively validated in the manner possible for skin stimuli in the S series. The subject's report constitutes the primary evidence of his introspective experience. No other independent measure of such subjective timing is available, although some of the other available evidence can affect confidence in the validity of the observed timings; this is summarized below in point (3).

It is of course possible to conceive or postulate conditions that might introduce discrepancies between the actual and the reported initial times of such an awareness. For example, what if it were possible to judge accurately only the end of the mental event, the conscious urge to move; the actual time of its onset, in relation to a perceived clock-time, would then be unknown and in doubt. In relation to such a suggestion we note, first, that each subject was instructed to 'watch for' and report the earliest appearance of the awareness in question, and subjects did not raise any difficulties about doing this. Secondly, perceptual timings of onset and offset found for a peripherally induced sensation, at least, do not support the suggestion that only the end is accurately judged. Using a method of cross-modality simultaneity judgements, Efron (1973) found that (a) there was no difficulty in distinguishing onsets from offsets; (b) the perceptual onset latency was constant regardless of large changes in duration of the stimulus; whereas (c) perceptual offset latency could in fact vary when stimulus durations were shortened to < 150 ms, with the change in offset latency probably originating, in part, in the peripheral sensory structures. Somewhat related findings on perceptual onset latencies are available for a cerebrally induced mental event, elicited by a stimulus in the somatosensory system in man (Libet *et al.*, 1979). The mean differences between perceptual timings, for a brief skin stimulus relative to onset of a medial lemniscus stimulus lasting 200 ms, were only within a few tens of milliseconds. One might suggest that timing of an endogenous mental event, the spontaneously arising conscious intention to act, may be more difficult subjectively to pinpoint with accuracy than the timing even for the sensation elicited by an intracerebral stimulus in the medial lemniscus. The individual W values reported by our subjects in a given series of 40 events did show variability; but the difference between (onset of RP) and (mean W), in Table 1c, was consistently and considerably greater than the SE of mean W for the respective series. Actually, the converse possibility, of W times reported earlier than the actual time of awareness of the urge to move, presented a more real difficulty. A 'preawareness' that one is preparing to perform the voluntary act, sometime within the next second or so, does in fact accompany at least some of the events in those series that produce a type I RP, as noted above (Libet *et al.*, 1982). If such a preawareness were to have affected the report, it would mean that the reported W times were more negative, earlier, than they should have been; the difference between onset of RP and 'real' W should then be even greater than indicated by our results. However, in series giving type II RPs, all of the self-initiated acts were described as 'spontaneous'; the subjects reported that each urge or wish to act appeared suddenly 'out of nowhere', with no specific preplanning or preawareness that it was about to happen.

Finally, the possibility could be raised that an earlier nonrecallable phase of the conscious urge exists, one that is not storable as a short-term memory. If it is further assumed that the subject's report of W time requires short-term memory of the mental event, then the reported time would apply only to a later, recallable phase of awareness, given such assumptions. First, one should note that, to report W time, the subject needed to recall only the clock-position of the revolving spot at the time he became aware of the urge/intention to move, and not necessarily the conscious mental event itself. (Actually, the latter was at least often recallable, as the subjects were able to describe it, even in relation to experiences just preceding it during the trial.) Secondly, the proposal of a nonrecallable initial phase of the conscious urge to move is a hypothetical construct which, like some other potential uncertainties in timing an endogenous mental event, is at present not directly testable. Thus, although it cannot be definitively excluded, it also lacks experimental support.

(3) *Additional evidence bearing on the validity of the reported timings.* One way to test and improve confidence in the validity of the reported timings lies in using different but converging modes of observing and reporting, with each mode having independent validity without further assumptions (*see* Garner, 1954, for discussion of this approach in connection with a related issue). Two quite different modes were employed for reporting the 'clock-positions' of the CRO spot at the time of awareness, that is, the absolute (A) reading *vs* the order (O) relative to final spot positions. Yet both modes produced values for W in the same range and were essentially indistinguishable. (This also held for reported timings in the M and S series.)

Subjects definitively distinguished the experience and time of awareness of wanting to move (W) not only from those of a skin sensation (S) but also from awareness of actually moving (M). Mean values for W times were consistently negative (by $>$ 100 ms on average) to those for M times (Tables 1A, 2D). This was true in spite of the unexpected finding that mean M values were themselves generally negative to EMG zero time, although they were only slightly negative to S values in which no movement was involved. M has some features of an endogenous mental event, rather than simply of a sensation elicited by input from peripheral sensory sources (*see below*, for discussion of M preceding the EMG). On the other hand, onset-times for type I or II RPs in series asking for W reports were generally similar to those asking for M reports, or even to those in series when no reports of awareness were requested (*see also* Libet *et al.*, 1982). This indicates that the somewhat different mental sets associated with each kind of reporting (or absence of reporting) did not affect the RP side of the time differential with respect to W.

It might be argued that subjects' reports of W times could be distorted by their awareness of the time of the actual movement; this might induce them to report W times that are later than the actual time of appearance of the conscious intention to move. But the subjects confirmed that for W reports they concentrated on noting their *earliest* awareness of any urge/intention to move. They further stated that their mental set for 'observing' W time was also different from that for M time.

Furthermore, the available evidence indicates that the subjects' experience with attending to the awareness of actually moving (M) may have induced them to report W times that were somewhat more, not less, negative relative to EMG zero time (*see* Results, end of Section I). The mean W values were on the average about 50 ms more negative when, in a given session, the W series was performed after instead of before an M series (*see* Table 2D, etc.).

Awareness of 'actually moving' (M) preceded the EMG. Mean M values were generally negative to EMG zero time for most subjects, and consistently though slightly negative (average about −40 ms) relative to S values for all subjects. Timing of M so as to precede the activation of muscle contraction indicates that M was not reflecting awareness of proprioceptive sensory impulses elicited by the movement. It suggests the possibility that M reflected an awareness associated more immediately with initiation of efferent cerebral output for the movement. Components that follow the main negative RP shift are recordable just prior to movement, including a negative 'motor potential' that begins about 50 ms before the EMG (*see* Deecke *et al.*, 1976; Shibasaki *et al.*, 1980).

Unconscious and Conscious Initiation or Control of Voluntary Acts

Since onset of RP regularly begins at least several hundreds of milliseconds before the appearance of a reportable time for awareness of any subjective intention or wish to act, it would appear that some neuronal activity associated with the eventual performance of the act has started well before any (recallable) conscious initiation or intervention could be possible. Put another way, the brain evidently 'decides' to initiate or, at the least, prepare to initiate the act at a time before there is any reportable subjective awareness that such a decision has taken place. It is concluded that cerebral initiation even of a spontaneous voluntary act, of the kind studied here, can and usually does begin *unconsciously*. The term 'unconscious' refers here simply to all processes that are not expressed as a conscious experience; this may include and does not distinguish among preconscious, subconscious or other possible nonreportable unconscious processes.

A general hypothesis had already been proposed that some substantial time period of appropriate cerebral activity may be required for eliciting all specific conscious experiences (Libet, 1965). This developed out of experimentally based findings that cortical activities must persist for up to 500 ms or more before 'neuronal adequacy' for a conscious sensory experience is achieved (*see* Libet, 1966, 1973, 1981*a*; Libet *et al.*, 1972). In that hypothesis, those cerebral activities that did not persist sufficiently would remain at unconscious levels. The present evidence appears to provide support for that more general hypothesis. It suggests that a similar substantial period of cerebral activity may also be required to achieve 'neuronal adequacy' for an experience of conscious intention or desire to perform a voluntary act.

The present evidence for the unconscious initiation of a voluntary act of course applies to one very limited form of such acts. However, the simple voluntary motor act studied here has in fact often been regarded as an incontrovertible and ideal example of a fully endogenous and 'freely voluntary' act. The absence of any larger meaning in the simple quick flexion of hand or fingers, and the possibility of performing it with capriciously whimsical timings, appear to exclude external psychological or other factors as controlling agents. It thus invites the extrapolation that other relatively 'spontaneous' voluntary acts, performed without conscious deliberation or planning, may also be initiated by cerebral activities proceeding unconsciously.

These considerations would appear to introduce certain constraints on the potential of the individual for exerting conscious initiation and control over his voluntary acts. However, accepting our conclusion that spontaneous voluntary acts can be initiated unconsciously, there would remain at least two types of conditions in which conscious control could be operative. (1) There could be a conscious 'veto' that aborts the performance even of the type of 'spontaneous' self-initiated act under study here. This remains possible because reportable conscious intention, even though it appeared distinctly later than onset of RP, did appear a substantial time (about 150 to 200 ms) before the beginning of the movement as signalled by the EMG. Even in our present experiments, subjects have reported that some recallable conscious urges to act were 'aborted' or inhibited before any actual movement occurred; in such cases the subject simply waited for another urge to appear which, when consummated, constituted the actual event whose RP was recorded (Libet *et al.*, 1982). (2) In those voluntary actions that are not 'spontaneous' and quickly performed, that is, in those in which conscious deliberation (of whether to act or of what alternative choice of action to take) precedes the act, the possibilities for conscious initiation and control would not be excluded by the present evidence.

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SPONTANEOUS EYE-BLINK RATES AND DOPAMINERGIC SYSTEMS

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SUMMARY

A series of studies demonstrated a possible relationship between eye-blink rate and central dopamine activity. First, apomorphine and other dopamine agonists acutely increased blink rate in monkeys, an effect blocked by sulpiride. Secondly, parkinsonian patients with levodopa-induced dyskinesia exhibited twice the mean blink rate (21 blinks/min) of other parkinsonians (11 blinks/min, $P < 0.002$) whereas the more symptomatic of the nondyskinetic patients had a very slow rate (3 blinks/min, $P < 0.01$). Thirdly, schizophrenic patients had an elevated mean blink (31 *vs* 23 blinks/min for normals, $P < 0.05$) which was normalized by neuroleptic treatment. Thus, the correlation with central dopamine activity may also prove clinically useful in selected neuropsychiatric disorders.

INTRODUCTION

Spontaneous eye-blink rates are decreased in Parkinson's disease (Hall, 1945), a condition associated with decreased central dopaminergic activity (Hornykiewicz, 1974), suggesting that blink rates may be mediated by central dopaminergic activity. Blinking could therefore be a useful clinical monitor of the functional state of this neurotransmitter. Moreover, blinking is readily quantified and can be observed even in the most uncooperative patients.

In this report we describe an initial series of studies which measure the effects of central dopaminergic agents, and various activities such as reading and speaking, on spontaneous blink rates. Blinking is then examined in Parkinson's disease and schizophrenia. To do this we investigated blink rates in four groups of subjects: (1) monkeys; (2) normal controls; (3) patients with Parkinson's disease; and finally (4) schizophrenic patients.

Spontaneous eyeblinks in primates, including humans, were defined as bilateral paroxysmal brief repetitive eye closures that occur continuously and in the absence of obvious external stimuli.

ANIMAL STUDIES

In our initial animal study, we administered the dopamine agonist, apomorphine, to 4 rhesus monkeys (Karson *et al.*, 1981*a*). A dose of 0.36 mg/kg administered subcutaneously quadrupled the blink rate (fig. 1) ($\chi_r^2 = 16.00$, $P < 0.01$) 30 min after injection. Casey *et al.* (1980) reported similar findings with a dose of 0.25 mg/kg. Because apomorphine has actions on other neurotransmitter systems (serotoninergic) and multiple types of dopaminergic receptors (Kebabian and Calne, 1979), additional drugs were administered to clarify further the role of dopamine in regulating eye-blink rates.

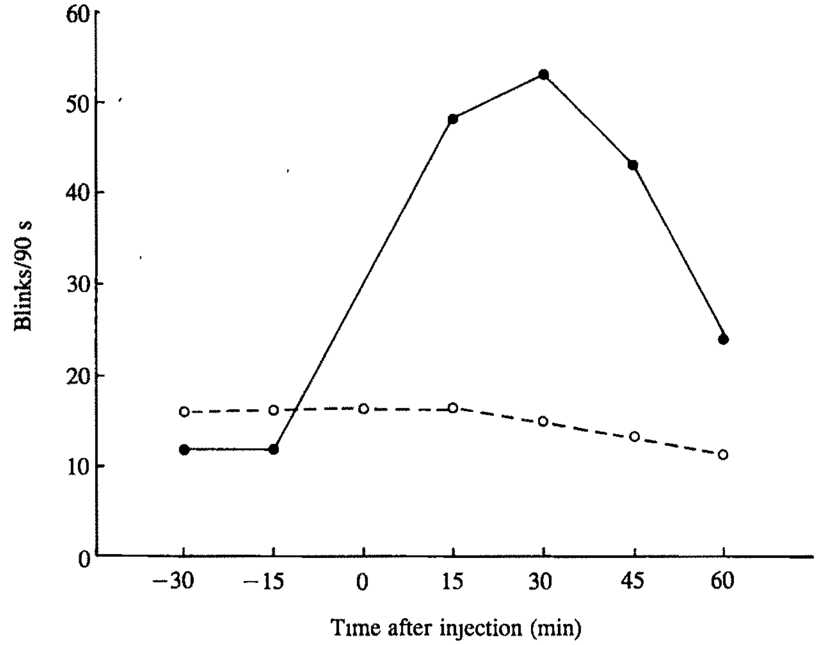

FIG 1. The acute effect of apomorphine (0.36 mg/kg, s.c.) on blink rates in rhesus monkeys ($\chi_r^2 = 16.00, P < 0.01$). Closed circles (solid line) represent apomorphine and open circles (dashed lines) represent saline. Haloperidol pretreatment (1.0 mg/kg i.m. 3 h prior to apomorphine) blocked this response. Low dosages of apomorphine (0.02 mg/kg) did not increase blink rates. Each point represents the mean of 4 animals.

Methods. The subjects were 4 adult male *Macaca fascicularis* monkeys weighing between 4.5 and 6.8 kg. Four categories of drugs were administered: (1) those affecting dopaminergic neurons, including dopamine, apomorphine, bromocriptine, haloperidol and sulpiride; (2) the cholinergic agents atropine and physostigmine; (3) drugs which affect alpha-noradrenergic transmission, including clonidine, phenylephrine and phentolamine; and (4) miscellaneous drugs including lysergic acid diethylamide (LSD) and diazepam. Apomorphine and phenylephrine were administered subcutaneously (s.c.) and all other drugs intramuscularly (i.m.). The injection volume was 0.5 ml.

The method for observing the effect of drugs on blinking in monkeys has been described previously (Karson *et al.*, 1981*a*). Blinks were observed and counted by direct observation by an observer, blinded to the drug and its dosage, for 90 s at 2 preinjection (−30 and −15 min) and 4 postinjection intervals (+15, +30, +45, +60 min).

A single dose of a particular drug was administered every other weekday to a pair of animals. A trial of each drug consisted of different doses given in random order, with two weeks allowed to elapse before the procedure was repeated for a different drug. The dose response for a particular drug was analysed by Friedman's two-way analysis of variance (Siegel, 1956) utilizing the difference between the baseline (mean of observations at −30 and −15 min) and the postinjection blink rate for each dose for each animal at one postinjection interval.

TABLE 1 THE EFFECT OF DRUGS ON SPONTANEOUS EYE-BLINK IN MONKEYS

	Postinjection interval			
Drug	*+15 min*	*+30 min*	*+45 min*	*+60 min*
Apomorphine	—	↑*	↑*	—
Bromocriptine	—	—	—	↑*
Atropine	↑**	↑*	—	—
Physostigmine	—	↓*	—	—

* $P < 0.05$ Friedman's two-way analysis of variance. ** $P < 0.01$. ↑ = increased blink rate. ↓ = decreased blink rate. No effect was obtained with dopamine, clonidine, phenylephrine, phentolamine and LSD.

Results. Among dopaminergic drugs, significant dose-related increases in blink rate were observed for apomorphine and bromocriptine (Table 1). Atropine also significantly increased blink rates whereas physostigmine decreased blinking. Sulpiride, a D_2 blocker, obliterated the apomorphine-induced increase when administered 3 h prior to each apomorphine injection, at a dose of sulpiride of 20 mg/kg i.m. ($\chi_r^2 = 3.6$, $P > 0.3$).

Finally, the animals were treated with diazepam to examine the effect of nonspecific sedation. Three hours prior to the injection of the largest apomorphine dose (0.45 mg/kg) diazepam was given i.m. While diazepam did decrease the apomorphine response, this effect was not related to dose (fig. 2).

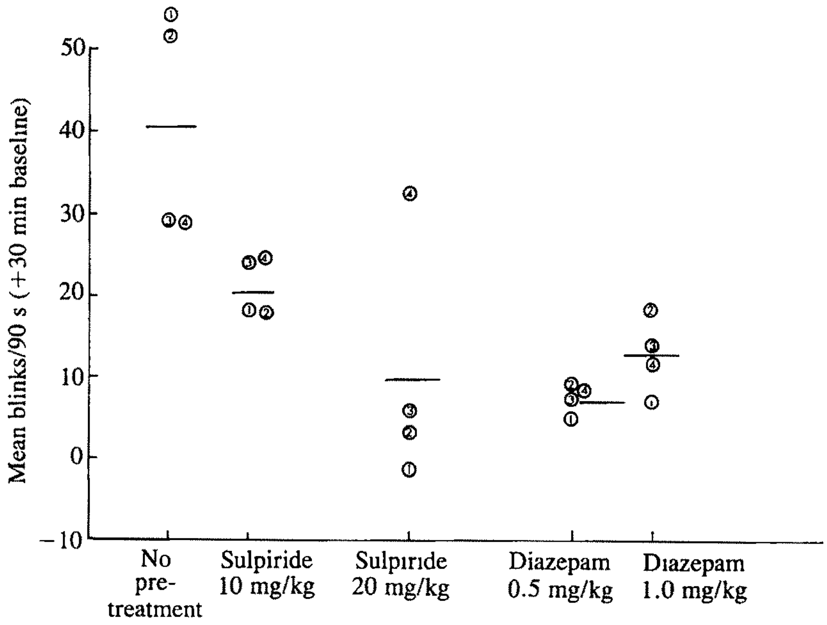

FIG. 2 Pretreatment of monkeys with sulpiride and diazepam inhibits the eye-blink rate increase induced by apomorphine (0.45 mg/kg). This effect is dose-related with sulpiride but not with diazepam. Each circle represents one animal.

Comment. The dose-related increase in blink rates elicited by the dopaminergic agonists apomorphine and bromocriptine, supports the hypothesis that dopamine augments spontaneous eye blinking. Dopamine, which does not cross the blood-brain barrier, did not increase blinking, indicating that blink rates are modulated by an effect of dopamine on the central nervous system (CNS). The effects of atropine and physostigmine also indicate a possible role for the cholinergic system.

CLINICAL STUDIES IN NONSCHIZOPHRENIC SUBJECTS

Neuroanatomical and Physiological Control of Blinking

Reflex blinking is elicited by a variety of corneal stimuli, the glabella tap (Myerson's sign) and a variety of sudden sensory stimuli. This reflex is generally regarded as a trigeminofacial reflex (Kugelberg, 1952; Rushworth, 1962), although recent evidence also suggests a role for the facial nerve in the afferent arc (Willer and Lamour, 1977; Csecsei, 1979). There are two parts to the reflex, R1 and R2. R1 is a pontine reflex (Shahani and Young, 1972), while R2 travels a more complex route which includes the spinal pathway of the trigeminal nerve (Kimura and Lyon, 1972).

Spontaneous eye blinking is decreased in certain states where reflex blinking is increased such as parkinsonism (Pearce *et al.*, 1968) and infancy (Zametkin *et al.*, 1979). It is not affected by light, heat, humidity, or corneal anaesthesia and is normal even in the blind (Ponder and Kennedy, 1928) and elderly (Zametkin *et al.*, 1979).

Maintenance of the corneal tear film has an uncertain role in blinking. Since the tear layer is thin (6 to 10 μm), dry spots begin to appear 15 to 30 s after a blink (Doane, 1980). Blinks usually occur before the appearance of dry spots. Consequently the blink rate necessary to maintain ocular lubrication should be from 2 to 4 blinks/min, far below the normal adult blink rate (about 20 blinks/min, Karson *et al.*, 1981*b*). This indicates that factors other than corneal moisturization influence the spontaneous blink rate.

Blinking in Normals: the Effect of Mental Tasks

At least four factors other than corneal drying influence spontaneous blink rate: (1) reading; (2) mental state; (3) muscular tension; and (4) speech. A decreased blink rate occurs during reading (Peterson and Allison, 1931; Hall 1945); in contrast, the other factors are associated with blink rate increases.

An association between mental state and blink rate changes was initially demonstrated by Ponder and Kennedy (1928). It was noted that strong emotions, such as anger, increased blinking. Court witnesses had increased blinking during questioning, raising the possibility that anxiety or memory utilization could increase blink rates. A clear demonstration that increased blinking is associated with anxiety remains elusive (Meyer *et al.*, 1953). That blink rates are increased during memory tasks, however, has been substantiated (Tecce *et al.*, 1976).

Increased 'muscular tension' can increase blink rates (King and Michels, 1957). Malmo and Smith (1955) postulated and Martin (1958) reported an association between increased forehead tension and increased blinking, but not between blinking and tension in other parts of the body.

Another factor that can increase blink rate is speech (Hall, 1945). This could be related to simultaneous activation due to spread of innervation within the seventh cranial nerve, or it could be because speech is associated with mental functions which increase blinking.

Methods. The subjects were 49 members (29 males, 20 females, aged (mean ± SD) 36 ± 14 yrs) of the staff of the Division of Special Mental Health Research, Saint Elizabeth's Hospital, Washington, DC. Blinks were recorded electrographically as previously reported (Karson *et al.*, 1981*b*). Sharp high amplitude waves (greater than 50 μV and less than 1000 ms in duration were counted as blinks). After a 5 min accommodation period, blinks were measured during 4 conditions in the following order: (1) casual conversation with the examiner (3 min); (2) silence (3 min); (3) reading 5 cards with one proverb and 4 possible interpretations on each card; and (4) memorizing each of 2 paragraphs taken from the Wechsler Memory Scale, Form 1. Blinks were tabulated separately for the period which the examiner recited the paragraphs and when the subjects repeated them.

In 15 of the above subjects, we were able to observe their blink rates in staff meetings while they were sitting quietly, unaware that they were being observed. The intraclass correlation (Winer, 1971) for the blink rates measured in staff meetings and measured electrographically was 0.79. Because of the high correlation the two methods of blink counting were regarded as interchangeable.

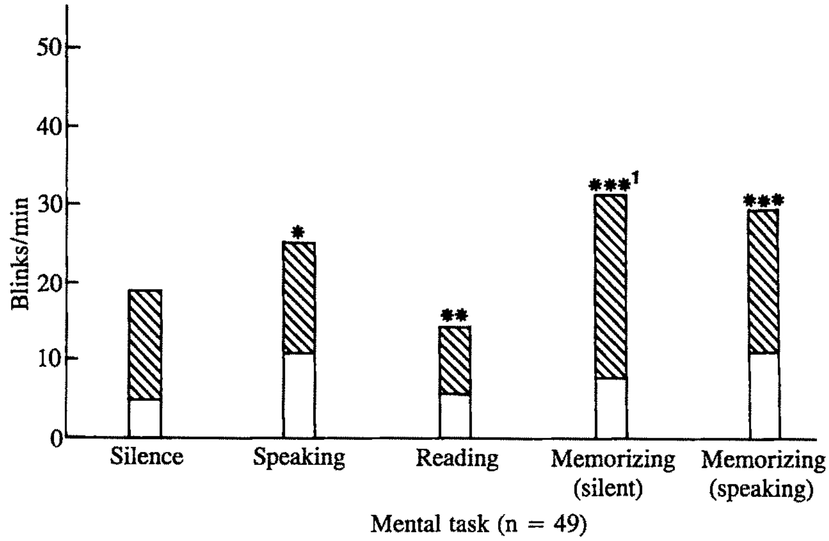

FIG 3. The effect of mental tasks on the mean eye-blink rate of 49 normal control subjects ($F_{(4,92)} = 20.28$, $P < 0.001$, one-way repeated measures ANOVA). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.0001$, compared with blink rate during silence by the Scheffé test. '1' = significant elevation ($P < 0.05$) as compared to blink during speech.

Results. The effect of mental tasks on blinking is illustrated in fig. 3 ($F_{(4,92)} = 20.28$, $P < 0.001$, one-way ANOVA for repeated measures) (Winer, 1971). The blink rate during reading (14 ± 8 blinks/min) was decreased as compared with the quiet blink rate (19 ± 14 blinks/min) ($t = 2.64$, $P < 0.01$; Scheffé test, Winer, 1971). Increased blink rates were recorded during speech (25 ± 14 blinks/min, $t = 2.46$,

$P < 0.001$) and during recitation of the paragraphs (29 ± 15 blinks/min, $t = 4.37$, $P < 0.001$. The blink rates recorded while the subjects listened to the memory paragraphs exceeded the blink rates during speech ($t = 2.6$, $P < 0.01$). Finally, the blink rate record during a 3 min period of speech immediately after the test had a high intraclass correlation (0.79, $P \leq 0.001$) with that recorded during the test.

Parkinson's Disease: Blinking and Dopaminergic Deficiency

In 1928, Ponder and Kennedy described extremely low blink rates in patients with Parkinson's disease. Hall (1945) found a mean speaking blink rate of only 11 blinks/min in postencephalitic parkinsonian patients, as compared to 25 blinks/min for controls. This reduction in blink rate may reflect the destruction of dopaminergic systems in the nigrostriatum in this disorder.

If blinking is linked to central dopaminergic activity, and central dopaminergic deficit parallels the severity of other manifestations of Parkinson's disease, then changes in both should covary. Consequently, the largest decrease in blink rates should be found in the most disabled patients. A second relevant clinical state is levodopa-induced dyskinesia. Since it has been suggested that this clinical state is due to increased central dopaminergic activity because of postsynaptic supersensitivity (Klawans, 1973), blink rates might be increased in patients with levodopa-induced dyskinesia.

Methods. The subjects were 61 parkinsonian outpatients of the Experimental Therapeutics Branch, National Institute of Neurological and Communicative Disorders and Stroke (39 males and 22 females; mean age 57 ± 11 yrs, mean duration of illness 11 ± 7 yrs). Three patients had never received dopamine agonist therapy and one patient was temporarily drug free. Of the remaining patients, 16 received levodopa in combination with carbidopa (Sinemet), 38 received a combination of Sinemet and a D_2 agonist (either bromocriptine, lisuride or pergolide) and 3 received D_2 agonist therapy only.

Blinks were counted by one observer (C.N.K.) during the initial 5 min of routine follow-up examinations: the mean blink rate for the 5 min was expressed as blinks/min. While subjects were sometimes informed that 'certain movements' were under observation, blinks were not specified.

Using criteria modified from Hoehn and Yahr (1967) the illness of each patient was staged according

TABLE 2 THE EFFECT OF STAGE OF DISABILITY AND LEVODOPA-INDUCED DYSKINESIA ON BLINK RATE (BLINKS/MIN)

Stage of disability	*I*	*II*	*III and IV*[a]	*Total*
Dyskinetic parkinsonism (n = 30)	15[b]	26	19	21*
Nondyskinetic parkinsonism (n = 31)	14	10	3[c]	11
Total	15	22	12	

[a] The higher numerals correspond to more severe parkinsonian symptoms (Hoehn and Yahr, 1967).

[b] The means are adjusted for mean duration of illness; consequently no standard deviation is given.

[c] Significantly decreased compared with nondyskinetic stage I ($t = 3.00$, $P < 0.01$) and Stage II ($t = 2.08$, $P < 0.05$) by the Scheffé test. * Significantly increased compared with the blink rate of nondyskinetic patients ($F_{(1,55)} = 11.4$, $P < 0.002$. For patients with levodopa-induced dyskinesia the effect of stage is not significant ($F_{(2,22)} = 2.43$, $P > 0.1$, one-way ANOVA in contrast to patients without dyskinesia ($F_{(2,22)} = 3.73$, $P < 0.05$).

to degree of disability. Stage III and IV patients were grouped because of the limited number of such patients. There were no Stage V patients.

The presence of levodopa-induced dyskinesia at the time of blink counting was determined according to the Abnormal Involuntary Movement Scale (AIMS) (1976).

Results. Parkinsonian disability significantly influenced blink rates for the whole patient group ($F_{(2,54)} = 2.53$, $P < 0.05$, one-tailed assumption, one-way ANOVA). This relationship was not present in dyskinetic parkinsonians, whose blink rate was double that of other patients (Table 2). Stage of disability and dyskinesia did not interact significantly ($F_{(2,81)} = 2.72$, $P > 0.07$, two-way ANOVA).

Fifteen patients were observed during both dyskinetic and nondyskinetic periods. The mean blink rate for these patients while dyskinetic was 24 ± 16 blinks/min, and that during the nondyskinetic state was 16 ± 11 blinks/min ($P < 0.001$, fig. 4).

To examine the relationship between severity and locale of dyskinesia and blink rate, blink rates from patients during the dyskinetic periods were correlated separately with the dyskinesia score for the facial muscles and the limb-truncal areas. There was a slight but significant positive correlation with facial dyskinesia score ($r = 0.35$, $P < 0.05$), but not the limb truncal score ($r = 0.06$, $P = 0.75$),

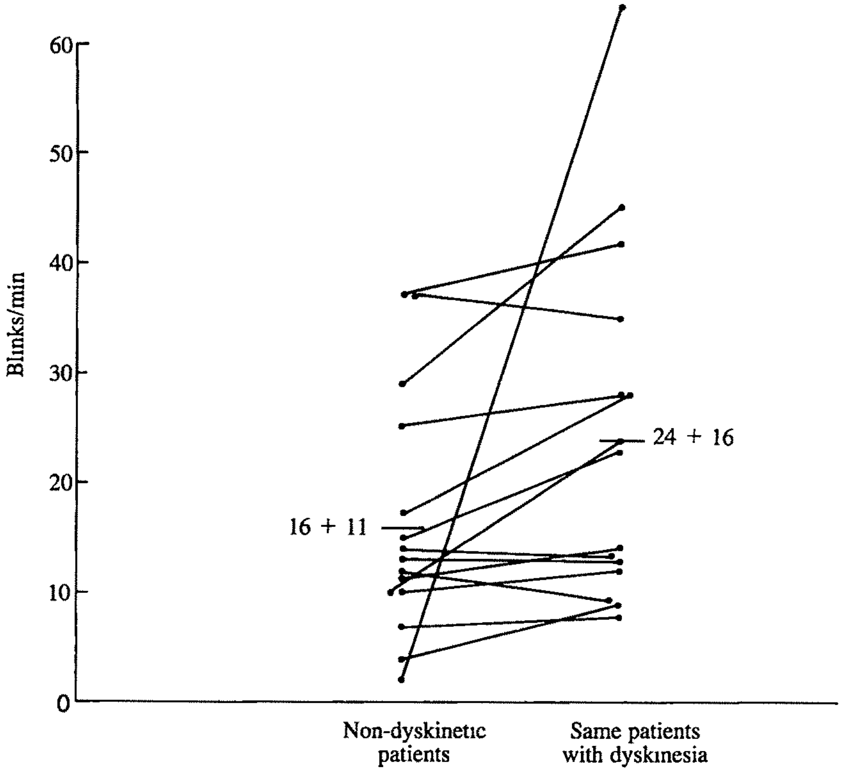

FIG. 4. Blink rates were increased in the same patients during active episodes of levodopa-induced dyskinesia (means ± SD) ($t = 11.00$, $P < 0.001$, Wilcoxon test).

indicating that the severity of the facial dyskinesia exerts a significant but limited influence on blink rate in these patients.

Comment. Our hypothesis that blink rates are mediated by central dopaminergic activity is consistent with the greater reductions of blink rate in patients with more severe Parkinson's disease, and the increased rate found in patients with levodopa-induced dyskinesia. These relationships raise the possibility that blink rate might be a useful clinical monitor in judging optimum drug treatment in Parkinson's disease.

SCHIZOPHRENIA: EXPLORING THE DOPAMINERGIC ASPECTS

Blink rates could be a useful measure of dopaminergic activity in schizophrenia, a condition in which it has been difficult to substantiate a proposed role for increased central dopamine activity (Carlsson and Lindqvist, 1963). This is tested in the next section.

Methods. The patients were 44 treatment-resistant chronic schizophrenic patients (Research Diagnostic Criteria; Spitzer *et al.*, 1978) including 34 males and 10 females (mean age for the group, 31 ± 7 yrs, range 19 to 47 yrs). The control group of 54 subjects was again derived from the staff of the Division of Special Mental Health Research, Saint Elizabeth's Hospital (34 males, 20 females, mean age 36 ± 7 yrs).

Blinks were counted by 2 observers equipped with stopwatches during clinical interviews. The time for each observation was 3 min and the average blink rate expressed as blinks/min. The intraclass correlation for blink counting between 3 independent observers on the same 17 subjects on the same day was 0.95 (Karson *et al.*, 1981*c*).

The 'drug-free' blink rate is the mean of all counts (usually weekly) made during the period of total drug withdrawal, which usually lasted six weeks (range 2 to 21 wks). The 'medicated' blink rate is the mean of all counts while the patient received only neuroleptics (and anticholinergics when necessary) both before and after the drug withdrawal period.

Blink Rates in Schizophrenic Patients

The first quantitative study of blinking in 'psychotic' patients was by Ostow and Ostow (1945), before the advent of phenothiazines. They reported increased mean blink rates in psychotic patients (27 ± 18 blinks/min) compared with other psychiatric patient groups (mean rates ranging from 18 to 22 blinks/min. This increase, however, is not statistically significant ($F_{(4,95)} = 1.42$, $P > 0.2$). Subsequently, Stevens (1978) reported increased blinking (defined as > 30 blinks/min) in 20 of 44 medication-free chronic schizophrenic subjects, all of whom had received prior neuroleptic therapy.

The mean blink rate for medication-free patients in the present study, 31 ± 17 blinks/min, significantly exceeded that of normal controls, 23 ± 15 blinks/min ($t = 2.25$, $P < 0.03$, fig. 5). As in Stevens' study, all these patients had received previous neuroleptic therapy.

Dopamine Antagonists (Neuroleptics)

Neuroleptic medications which are dopamine receptor antagonists reduced the mean blink rate of these patients to 24 ± 11 blinks/min (paired $t = 3.73$, $P < 0.001$).

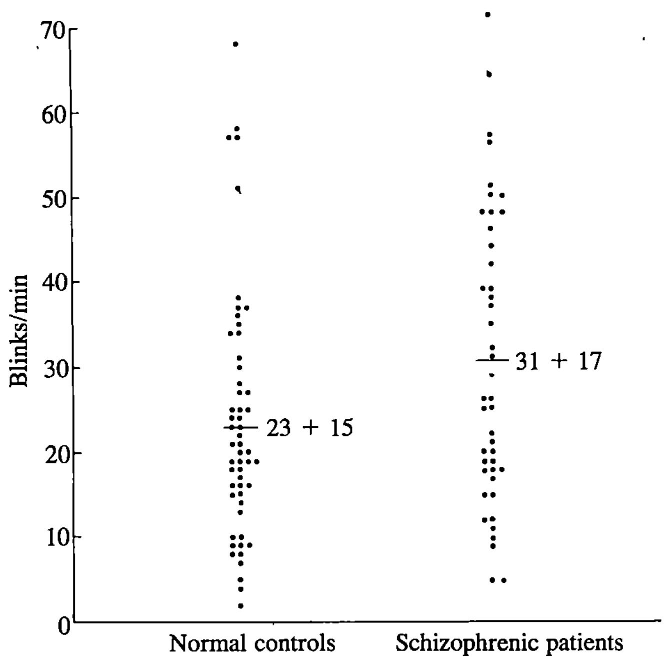

FIG. 5. Mean eye-blink rates are increased in medication-free chronic schizophrenic patients (n = 44) as compared with normal controls (t = 2.25, $P < 0.03$, n = 54).

A decrease (defined as a reduction of more than 1 blink/min) occurred in 26/43 patients.

Tardive Dyskinesia

The mean medication-free blink rate of 9 patients with tardive dyskinesia (according to the criteria of Jeste and Wyatt, 1982) was 32 ± 13 blinks/min, nearly identical to 30 ± 18 blinks/min recorded for schizophrenic patients without tardive dyskinesia. This may indicate that dopaminergic activity is not elevated in schizophrenic patients with tardive dyskinesia compared to those without, or that the elevations already seen in schizophrenia obscure the effect of dyskinesia. In contrast, the dyskinesia induced by levodopa increased blinking in parkinsonian patients.

CONCLUSIONS

Spontaneous eye-blink rates are readily observed and easily quantified. They appear to reflect the activity of the central dopaminergic systems, as well as concurrent mental activity. In two diseases involving abnormal dopaminergic activity, Parkinson's disease and schizophrenia, blink rates are decreased and increased respectively and are altered by variations in the status of each illness and their respective treatments. As such, blink rates are a useful clinical sign of central dopamine activity.

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DEFICITS IN ATTENTION AND MOVEMENT FOLLOWING THE REMOVAL OF POSTARCUATE (AREA 6) AND PREARCUATE (AREA 8) CORTEX IN MACAQUE MONKEYS

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SUMMARY

The effect of unilateral surgical ablations of the postarcuate cortex (area 6) has been studied in the macaque monkey (*Macaca irus*). Two series of neurological deficits were found: (1) a failure to grasp food with the mouth when presented contralaterally to the lesion and a reluctance to use the contralateral hand; (2) a severe hemi-inattention. This was present in both the somatosensory and visual modalities but, in the latter, was limited to the peripersonal space.

Both motor and attentional deficits improved with time. However, when the symptomatology was stabilized, the animals tended to use the ipsilateral hand and, when presented with two stimuli, preferred that ipsilateral to the lesion.

Control experiments in which area 8 (frontal eye fields) was ablated unilaterally showed a decrease of eye movements contralateral to the lesion and a neglect of the contralateral hemispace. No somatosensory deficits were found. The visual neglect was more prominent for 'far' space than for that near the animal.

The role of area 6 in organizing motor acts and the strict relation between the type of motor deficit and the type of neglect are discussed.

INTRODUCTION

The largest portion of the agranular frontal cortex of the primates is formed by the cytoarchitectonic area 6 (*see* Blinkov and Glezer, 1968). Structurally this area is not uniform and by taking into account small cytoarchitectonic differences, it can be subdivided into several subareas (Vogt and Vogt, 1919; von Bonin and Bailey, 1947; *see also* Barbas and Pandya, 1981). The issue of whether these subareas represent units with different functions is not solved, but there are three sets of data that indicate that area 6 is functionally inhomogeneous. In man, studies of regional blood flow have demonstrated that during different tasks, blood flow increases in a differential way in the medial and lateral parts of area 6. The former part appears to be related to self-generated programs of movements, the latter part to externally triggered programs (Roland and Larsen, 1976; Roland, Larsen *et al.*, 1980; Roland, Skinhøj *et al.*, 1980). Recordings of the activity of single neurons in the monkey have shown that neurons located rostrally on the lateral surface of area 6 can be driven by somatosensory and also visual stimuli (Rizzolatti *et al.*, 1981*a*, *b*; Godschalk *et al.*, 1981), whereas those located on the medial surface, including the supplementary motor area, are poorly driven by the same stimuli (Brinkman and Porter, 1979; Wise and Tanji, 1981). Finally, data obtained with tracing techniques (Muakkassa and Strick, 1979; Matsumara and Kubota, 1979) indicate that at least four somatotopic representations exist in area 6. Thus if the concept is accepted that an independent somatotopic representation is also an independent functional unit, area 6 contains at least four functional subareas.

In this paper we shall describe the effect of surgical lesions of one of the subareas of area 6, namely of that which, in the macaque, is located in the posterior bank of the arcuate sulcus and in the immediately adjacent cortex caudal to it (postarcuate premotor area). In previous experiments we have shown that neurons of this area can easily be activated by somatosensory and especially tactile stimuli (Rizzolatti *et al.*, 1981*b*). Neurons responding to stimulation of the mouth lie on the bank and the lip of the inferior arcuate sulcus while neurons driven by stimulation of the hand lie at, or very near the junction between the inferior and superior limbs of the sulcus. Few physiological data are available on the location of the leg representation but, according to the anatomical findings (Muakkassa and Strick, 1979), this should lie medial to the hand area.

Besides responding to somatosensory stimuli, many neurons of the postarcuate premotor area can be driven by visual stimuli. A particularly interesting property of these neurons is that, in order to be activated in a stable, reliable way, they require stimuli in the space immediately around the animal (peripersonal space). The visually responsive regions can be located very close to the animal (pericutaneous space) or more distantly, but still approximately within the animal's reaching distance (distant peripersonal space). The visual responding regions abutting upon the animal's skin are in register with the tactile fields (Rizzolatti *et al.*, 1981*c*).

On the basis of these and other receptive field properties of the postarcuate neurons we proposed that somatosensory and visual inputs are used by the postarcuate neurons to organize specific-input-related motor acts. The activity of the postarcuate neurons during motor behaviour appears to support this proposal (Rizzolatti *et al.*, 1981*a*). For example, in the mouth representation of the postarcuate premotor area, besides units not influenced by movements (postarcuate class 1 neurons), there are many that show a marked increase of their firing when sensory stimulation is followed by a particular motor act related to the stimulation (postarcuate class 2 neurons). Other units in the same region can be activated exclusively if the sensory stimulation is followed by a specific motor act such as grasping food with the mouth, biting or sucking. Movements where the same muscles are used but with other aims as in expressing emotion, are ineffective in triggering these units (postarcuate class 3 neurons).

The aim of the present experiments was to verify to what extent a unilateral ablation of the postarcuate motor cortex would affect specific motor acts. Two types of neurological deficits were found: (1) a transient incapacity to organize certain motor acts; (2) a severe hemi-inattention. This was present in both the somatosensory and visual modalities, and in the last was limited to peripersonal space. Control experiments in which we ablated area 8 (frontal eye fields) permitted us to exclude this area as being responsible for this particular visual neglect. A preliminary note on some of these findings has been published elsewhere (Rizzolatti *et al.*, 1980).

METHODS

Subjects and Operation

Five juvenile Java monkeys (*Macaca irus*) weighing less than 3 kg were used. After a period of shaping, all animals were examined neurologically and tested as described below. The testing was repeated several times and the last session before operation was recorded on videotape. Once the testing was completed the animals received a unilateral frontal lesion. The lesion was placed in the postarcuate premotor area in 3 monkeys (P monkeys), in the frontal eye fields in 2 monkeys (A monkeys). In 1 animal (P1) the posterior bank of the arcuate sulcus on the side opposite to that of the first lesion was ablated six weeks after the first operation.

The operations were performed under sterile conditions using ketamine anaesthesia. The lesions were made by subpial aspiration under microscope control using a narrow gauge sucker. At the end of the operation the dura was sewn and patches of 'fascia muscularis' taken from the superficial head muscles were sutured to the dura in order to achieve a complete closure of the dural plane. The bone was replaced, the muscle planes reconstructed and the skin sutured. All animals recovered within a few hours after the operation and were tested on the following day.

Testing

In addition to a general neurological examination we studied with particular care the animal's responses to stimuli (food or menace) located outside the animal's reach ('far' space), within the reach of its arms (distant peripersonal space) and around its mouth (pericutaneous buccal space). The testing was performed while the animal was sitting in a primate chair.

The *peribuccal space* was tested as follows. (1) A piece of food held by forceps was moved first in front of the mouth then on the right and on the left of it. The response consisted in a head movement towards the food accompanied by opening of the mouth and contraction of the facial musculature on the side where the food was presented. At the end of this motor act the food was grasped by the animal with its teeth. (2) Two pieces of food, kept initially close to one another, were moved simultaneously, one towards the right, the other towards the left from the centre of the mouth. (3) The blink response to menace was elicited. Testing was performed leaving the animal's arm free but preventing it from touching the food or the experimenter. This was achieved by increasing the length of the plexiglass plane around the animal's neck.

The study of *distant peripersonal space* was made by observing the orientating reaction of the monkey to food moved at about 30 cm from it, and by examining its capacity to reach for the food. Hand preference and accuracy of reaching was also studied by placing pieces of food of different size on a plane located in front, on the right, and on the left of the animal and observing how the food was grasped. The test was repeated using a plane with small holes on its surface. The food was placed inside the holes and the animal had to use its fingers in order to grab it.

Far space was tested as follows. (1) A piece of food held by a pair of forceps was moved at about 60 cm from the animal. (2) Two pieces of food, initially kept close one to another were moved simultaneously and then, when the animal was fixating them, were moved first laterally and then towards the animal. (3) An abrupt presentation of a stimulus was made when the animal was fixating another stimulus. The normal response was an orientating reaction towards the new stimulus. In the case of threatening stimuli the response was accompanied by a grimace expressing rage or fear.

At the end of the visual testing the mouth responses to *tactile stimulation* with food were studied. The response to stimulation of the lateral part of the mouth consisted of the coordinated head-mouth movements analogous to those evoked by visual stimuli moved in the peripersonal space. The test was undertaken both with the eyes open and closed. The responsiveness of the mouth to tactile stimuli was also tested by dropping some water on the upper lip. The stimulus elicited an immediate and precise licking of the wet part.

All animals were tested on the first, and, some, on the third day after operation; subsequently they were retested once a week until they were killed. The postoperative behaviour during the various tests was recorded on videotape. The animals' behaviour in their home cage was observed, but not video-recorded.

Histology

When the neurological deficit had become stable, the animals were killed. They were deeply anaesthetized with ketamine and then perfused through the heart, first with 0.9 per cent saline and then with 10 per cent formalin in normal saline. The skull was opened and the dura incised. Photographs of the brain were taken to record the sulcal pattern. After the brains had been hardened in formalin, blocks of tissue containing the cortical lesion and the thalamic nuclei connected with the lesioned areas were cut coronally on a stereotaxic frame. The blocks were further hardened in formalin and then embedded in parlodion (Monkeys P1, P2, A3) or in paraffin wax (Monkeys A2, P3). The brains embedded in parlodion (studied at the Department of Anatomy of the University of Pennsylvania by J. M. Sprague) were stained with cresyl violet and the Woelke-Heidenhain method, those embedded in paraffin wax (studied in Parma) were stained with cresyl violet and the Weil stain. Both series of brains were cut coronally at 40 μm. Every tenth section was stained with the Nissl stain and every eleventh by the Woelke-Heidenhain or Weil method. The extent of each cortical lesion was reconstructed in detail in projection drawings of selected coronal sections through the cortex and the thalamus (*see* Sprague *et al.*, 1977). The topography and terminology of the thalamic nuclei were taken largely from Olszewski (1952).

RESULTS

Lesions of the Postarcuate Premotor Area

The lesion of the postarcuate premotor area produced clear deficits in all animals. We shall describe first and in some detail the symptomatology of one monkey (P2) which can be considered representative of the whole group. The deficits observed in the other animals will be presented in a more schematic way.

Monkey P2. The extent of cortical ablation and thalamic degeneration found in this monkey is shown in fig. 1. As can be seen, the cortical lesion was very small and, with the exception of limited damage to area 8, restricted to the posterior bank of the arcuate sulcus. According to our electrophysiological data the ablated cortex corresponded to the part of postarcuate premotor area where neurons respond to the stimulation of the mouth and the hands.

The *first day* after operation the monkey's behaviour in its home cage was indistinguishable from that before the operation except that the right hand was used less often. When tested on the same day in the primate chair, this animal did not show any visual deficit for stimuli presented in 'far' space and in distant peripersonal space. Stimuli introduced on the right or on the left of the fixation point were immediately detected and the presentation of two simultaneous stimuli, one ipsilateral, the other contralateral to the lesion did not produce any side preference.

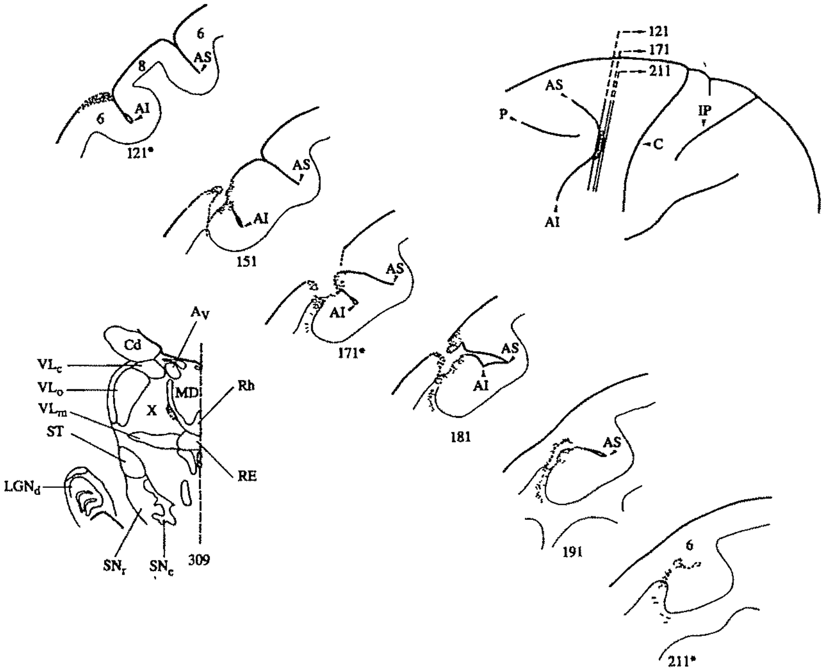

FIG. 1. Reconstruction from 40 μm sections of the cortical lesion and of the thalamic degeneration in Monkey P2 The sections are coronal. They were progressively numbered and the respective number is shown near each section. For abbreviations not indicated in the legend *see* the abbreviation list on pp. 670–671. Broken line = edge of lesion. Doted areas = denervated cortex, demyelinated white matter and thalamic degeneration. *after number = sections whose level is shown on brain drawing. AS = arcuate superior. AI = arcuate inferior. C = central. IP = intraparietal P = principal.

When stimuli were introduced in distant peripersonal space the monkey consistently reached for them using the hand ipsilateral to the lesion. Only when this hand was blocked or the food located outside its reach did the animal, although reluctantly, employ the contralateral hand. There was no misreaching, but the movement was somewhat slower than with the normal arm. There was also some clumsiness of finger movements, but in spite of this the animal was able to pick up small pieces of food with its fingers.

The most striking deficit was observed in the pericutaneous space around the mouth (peribuccal space). When the animal was fixating a central stimulus, the introduction of a piece of food ipsilateral to the lesion produced, as in normal animals, an immediate mouth grasping response; the same stimulus shown contralaterally was ignored. The rapid movement of a stimulus from the centre of the mouth to the contralateral side did not elicit any reaction, and subsequent movement of the stimulus in this part of peripersonal space was neglected. When a stimulus was moved slowly from a central position near the mouth to the neglected side, the animal appeared to be aware of the stimulus and tended to follow it but had great difficulty in organizing the appropriate head and mouth movement necessary for grasping it. Most commonly the animal slowly opened its mouth and followed the stimulus with the mouth open but without trying to take the object. When lateral grasping occurred, it was executed in a stereotyped way without the richness of buccal and facial movements observed on the other side.

When two stimuli were simultaneously moved in the peribuccal space the monkey always tended to reach for the one ipsilateral to the lesion. Occasionally there was a curious dissociation between the movements of the eyes and the head. The eyes in these cases followed the stimulus moving contralaterally, while the head and the mouth were attracted by that ipsilateral to the lesion.

Deficits similar to those demonstrated with visual stimuli were present when the hemiface and especially the half of the mouth contralateral to the lesion was stimulated with tactile stimuli. Stimulation of the lips with food or other stimuli produced either no response or the opening of the mouth not accompanied by any attempt to bite. Similarly the raising of the corner of the lips as well as the other facial movements which normally accompany food grasping with the mouth were absent. Licking movements could not be elicited by wetting the contralateral lip with water or juice; a similar stimulation promptly evoked the response on the ipsilateral side. There were no tactile deficits in response to stimuli applied to the limbs or the trunk as well as no motor deficits of any kind with the exception of those described above. Blinking to threatening stimuli moved towards the contralateral hemiface was absent. In contrast, facial movements were easily elicited by emotional stimuli presented far from the animal. Similarly the eye movements, which were hard to trigger with tactile or peribuccal stimuli, were easily elicited with visual stimuli presented far from the monkey.

Fifteen days after the operation the hemineglect was much less severe than immediately after the operation. Tactile stimuli were usually responded to and one visual stimulus (food) moved in the peribuccal space frequently elicited an attempt to reach it in the previously neglected space. When two stimuli were simultaneously moved in the peribuccal space the animal always preferred that ipsilateral to the lesion. The motor deficits also improved. The lateral mouth grasping, however, was slow on the side contralateral to the lesion and the facial movements that accompany this motor act were practically absent. The blinking reflex on the neglected side was reduced, but not absent. Slowness of movement of the right arm was still present, although reduced.

Sixty days after the operation the only residual deficits were the preference in using the hand ipsilateral to the lesion and a constant turning, in the test with two peribuccal stimuli, towards that ipsilateral to the lesion. It is interesting to note that when two stimuli were moved slowly the animal noticed both of them. This was shown by the fact that the monkey, after taking food in the normal hemispace, turned immediately to that contralateral to the lesion. The dissociation between eye and head movements, observed occasionally in the test during the first few days after the lesion, was frequent in this phase. The monkey was killed at the seventieth day after the ablation when the symptomatology was the same as at sixty days.

Monkey P1 (*left-sided lesion*). This monkey received two successive lesions in the postarcuate premotor area. The first was placed in the left postarcuate area, the second in the same area but on the right. The reconstruction of the left cortical lesion and the consequent thalamic degeneration are shown in fig. 2. The cortical lesion was slightly larger in the rostrocaudal direction than for monkey P2 and there was some involvement of area 8. No degeneration of the medial thalamic nuclei was observed.

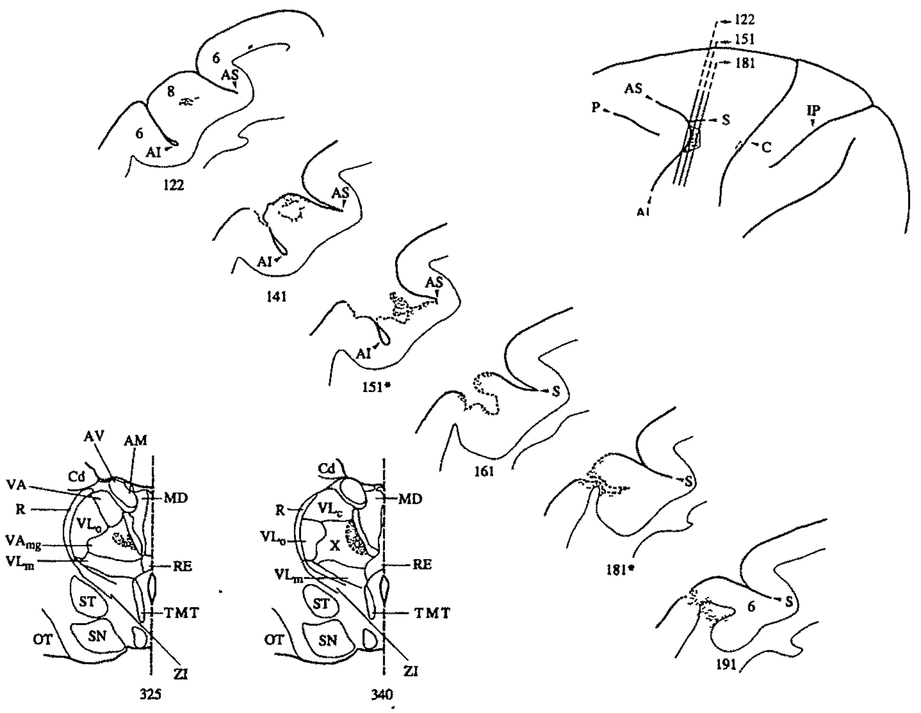

FIG. 2. Reconstruction of the left cortical lesion and of the thalamic degeneration in Monkey P1

The deficits consequent on the first lesion were very similar to that of Monkey P2. There was a clear contralateral attention deficit to stimulation of the mouth and the space immediately around it. As in Monkey P2 the coordinated head-mouth-face movements necessary to grasp the food in the contralateral hemispace were lacking. The only significant difference between Monkeys P2 and P1 was the absence in the latter of motor deficits of the contralateral hand. This was probably due to the fact that the whole lesion in P1 was located below the spur of the arcuate cortex, that is, lateral to the hand representation. Recovery after the lesion was faster in Monkey P1 than in P2. One month after the operation (last day of testing) the only deficits were a clear preference for ipsilateral stimuli in the peribuccal space in the two stimuli test and a less prompt blinking response to contralateral threatening stimuli. Six weeks after the first lesion the animal underwent a second operation on the right side.

Monkey P1 (*right-sided lesion*). Fig. 3 shows the location and the extent of the lesion on the right. In this case there was involvement of the white matter deep to area 6. The thalamic degeneration in the ventrolateral nuclear complex was diffuse and there was some cellular loss in the pars multiformis of the nucleus medialis dorsalis.

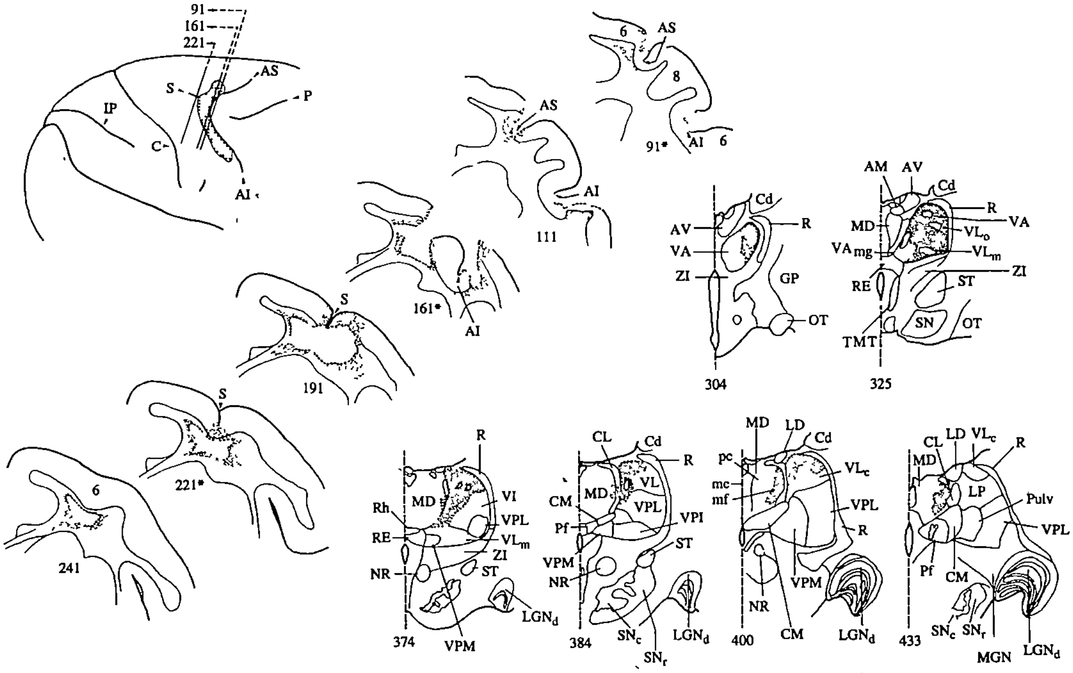

FIG. 3. Reconstruction of the right-sided cortical lesion and of the thalamic degeneration in Monkey P1

Neglect of peribuccal stimuli contralateral to the ablated side was very marked in this animal. Furthermore, and at variance with the other monkeys (P2, P1 left side, P3) P1 showed a preference for ipsilateral stimuli presented in far space and a paucity of saccadic eye movements towards the neglected side. These abnormalities are probably due to involvement of area 8 (*see below*). Tactile neglect was present. It was particularly severe for stimuli applied to the contralateral face, arm and hand and present, but less strong, on stimulation of the leg. The distal parts of the limbs were more affected than the proximal. Painful stimuli applied to the contralateral face, arm and hand produced a limited response and, when strong, gave rise to a general rage reaction rather than (as it occurred on the normal side) a specific response aimed at the removal of the stimulus.

There was a severe hypotonic paresis of the contralateral arm and a slight paresis of the contralateral leg and of the contralateral lower face. The monkey never used the left arm except during automatic movements such as walking and climbing. A clear postural asymmetry was evident when the animal was suspended in the air, the contralateral limbs hanging more than the ipsilateral arm and leg.

One month after the operation there was still neglect for stimuli applied to the face and, although very modest, to those applied to the hand. Visual neglect in the peribuccal contralateral space almost disappeared, but ipsilateral preference in the two stimuli test was very clear. There was no deficit for visual stimuli presented far from the animal. The contralateral (left) mouth grasping movement was slow and less dextrous than ipsilaterally. The left arm paresis remained severe and was accompanied by hypotonia; slight hypotonia was evident in the left leg, although the motor deficit had almost disappeared.

These abnormalities improved further with time. However, at the final testing (seventy-three days after operation) the animal still showed a marked preference for ipsilateral (right) stimuli in the two stimuli test in the peribuccal space, slowness in lateral mouth grasping accompanied by some poverty in facial movement, and a clear paresis of the contralateral (left) arm. The animal was killed a few days after this testing.

Monkey P3. The lesion in this animal was limited to the grey matter of the postarcuate premotor area. In comparison with Monkeys P2 and P1 (left side), the ablation extended more medially and included parts of postarcuate area lying above the junction between the superior and inferior arcuate sulci (fig. 4).

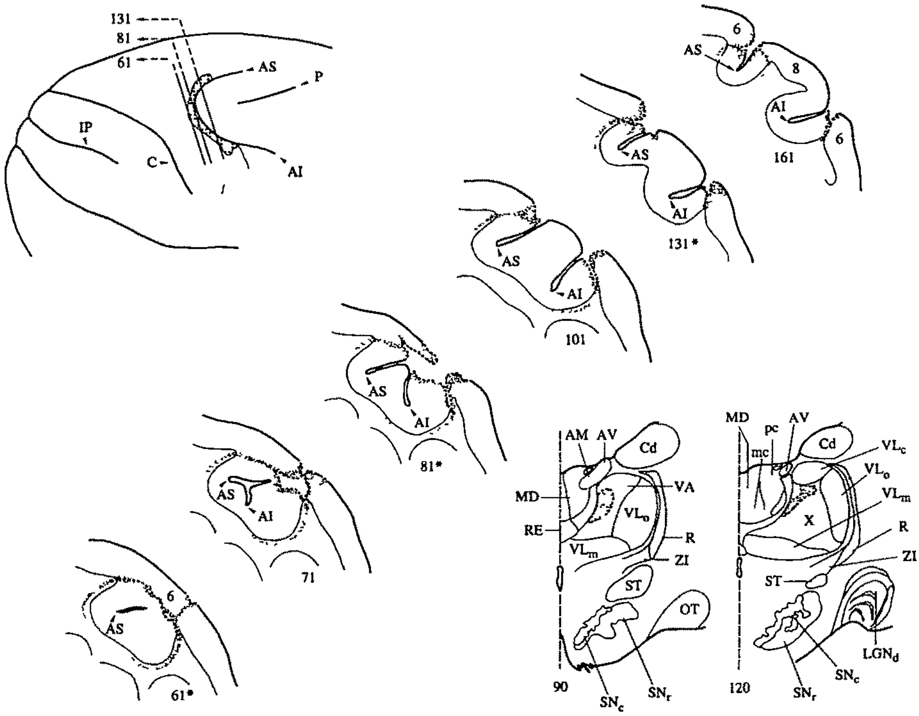

FIG. 4. Reconstruction of the cortical lesion and of the thalamic degeneration in Monkey P3.

The deficits were very similar to those of Monkey P2. In addition, there was a modest neglect for stimuli applied to the contralateral arm and leg. The recovery in this animal was fast. After forty-five days the only remaining abnormality was a clear preference, in the test with two peribuccal stimuli, for the stimulus moved in the space ipsilateral to the lesion.

Lesions of the Frontal Eye Fields

The basic pattern of the deficits following a lesion of the frontal eye fields in the monkey is well known (Bianchi, 1895; Kennard, 1939; Latto and Cowey; 1971; Watson *et al.*, 1978; Crowne *et al.*, 1981). However, as discrepancies exist between different reports on the presence of somatosensory neglect after this lesion, and also as a control for the posterior group, in two animals we ablated the anterior bank of the arcuate sulcus and the adjacent part of area 8 lying on the cortical convexity. As for the P group we shall describe the deficits of only one monkey in detail.

Monkey A2. The extent of the cortical lesion and of the thalamic degeneration in this animal is shown in fig. 5. The cortical lesion was fairly complete with no invasion of white matter. The damage to area 6 was minimal.

On the *first day* after the lesion, spontaneous ocular saccades and head movements towards the side contralateral to the lesion were very rare. When a visual

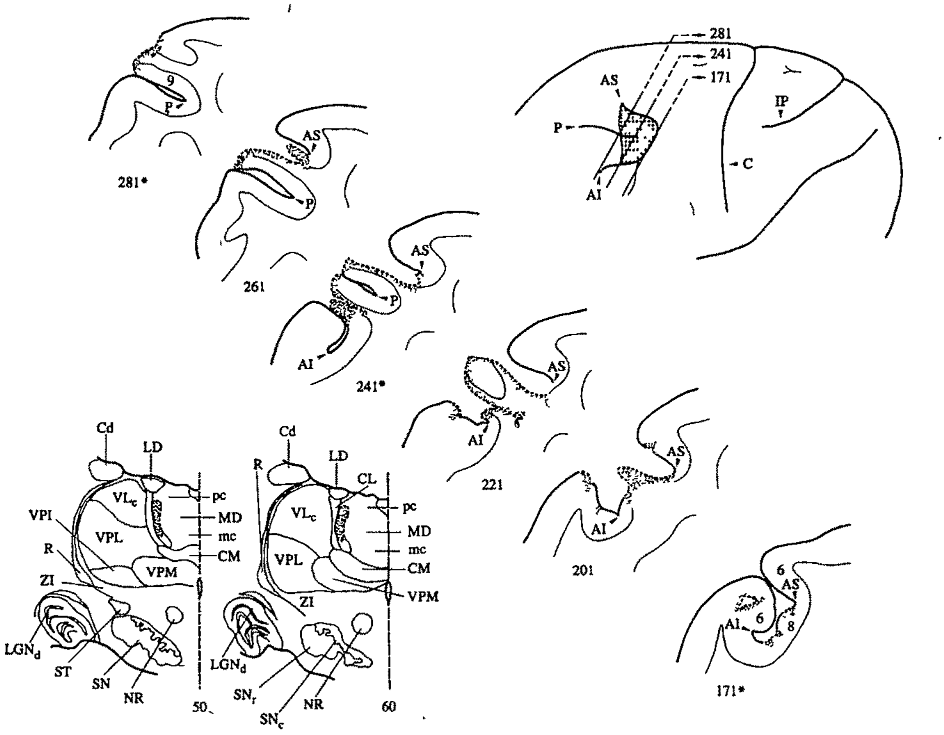

FIG 5. Reconstruction of the cortical lesion and of the thalamic degeneration in Monkey A2.

stimulus evoked a saccade in the neglected space, fixation of the stimulus was short and the eyes returned immediately to resting position. No tonic deviation of the head or the eyes was observed. However, when the animal was threatened with a central stimulus it usually turned ipsilateral to the lesion. Forced circling in a free situation was not observed.

Testing of far space showed brisk responses to stimuli presented ipsilaterally but, in contrast to the P monkeys, neglect of far stimuli presented contralaterally. The hemi-inattention was not absolute. When the animal was not paying attention to a central stimulus, a piece of food moved in the contralateral far space evoked response. The same was true for threatening stimuli in contralateral space. When two stimuli were simultaneously moved from a central position towards right and left, the contralateral one was always neglected.

In sharp contrast with posterior monkeys, the presentation of a stimulus in the peribuccal space evoked a precise mouth grasping movement also on the side contralateral to the lesion. The movement was accompanied by the normal pattern of facial muscle contraction. When two stimuli were moved in the space around the mouth, the ipsilateral stimulus was usually preferred. The blinking reflex to menace was absent on the right. There were no tactile or motor deficits and no hand preference was observed.

Fifteen days after operation the oculomotor disturbance, as judged clinically, had receded. There was also a clear improvement in attention deficits. Thus, for example, a piece of food introduced abruptly into the previously neglected space elicited a response even when the animal was fixating a central stimulus. If, however, two stimuli were simultaneously moved, the monkey without exception preferred that ipsilateral to the lesion. The same was true when many pieces of food were placed in front of the monkey and it was free to choose. In contrast to the preference for ipsilateral stimuli presented far from the monkey, no attention deficits were found for stimuli in the peribuccal space. Even in the test with two stimuli, a clear preference for the ipsilateral one was not observed.

After *one month* the only residual deficit was a preference for the ipsilateral stimulus in the test with two stimuli in far space. A modest preference for this side was present on the final testing (fifty-second day after operation).

Monkey A1. Fig. 6 shows the extent of the cortical lesion and of the thalamic degeneration in this animal.

The behavioural abnormalities were quite similar to those of Monkey A2. There was a clear contralateral attention deficit for stimuli presented far from the animal and a paucity of exploratory eye and head movements towards that side. Stimuli presented in the peribuccal space elicited the normal mouth grasping response on both sides and even with two stimuli it was hard to find a side preference. There were no motor or sensory deficits and no hand preference was observed. The only difference from the previous monkey was the faster recovery of this animal. After one month the monkey appeared to be clinically normal.

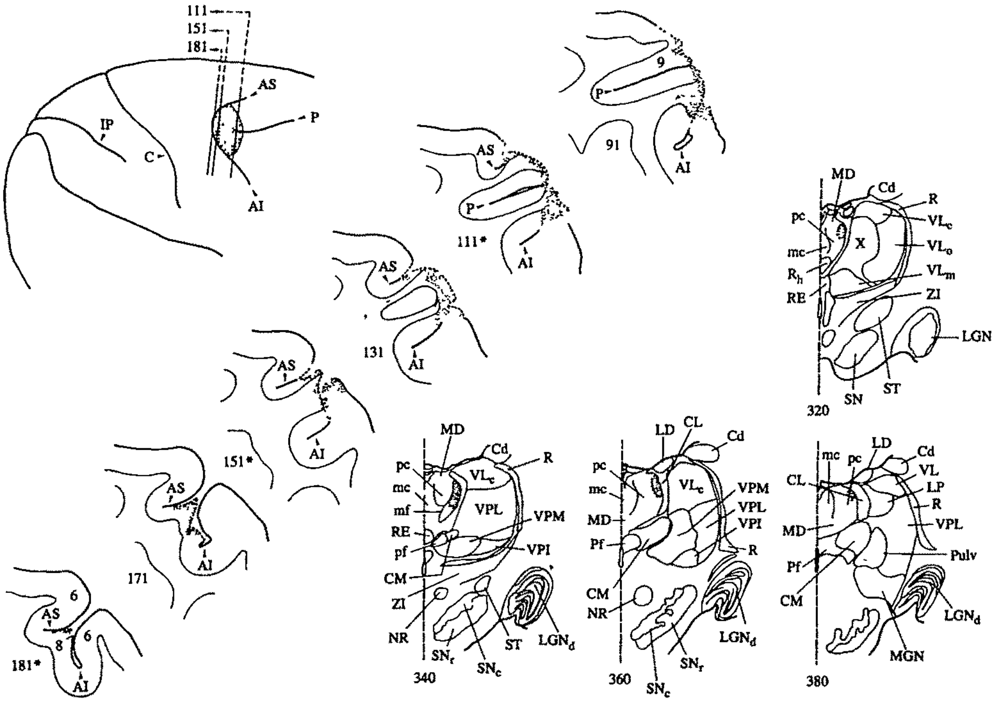

FIG. 6. Reconstruction of the cortical lesion and of the thalamic degeneration in Monkey A1.

DISCUSSION

It is a classical finding that lesions of area 6 affect very little the capacity of the animals to make elementary movements (Denny-Brown and Botterell, 1948; Fulton, 1949; Denny-Brown, 1966). In this respect the difference between damage in area 6 and in area 4 is striking. In area 4, a unilateral ablation of the arm representation induces a severe paresis affecting all movements of the contralateral arm (*see* Fulton, 1949), an ablation of the face representation produces a marked paresis of the contralateral lower facial musculature together with a slight widening of the contralateral palpebral fissure (Green and Walker, 1938). In contrast, a unilateral lesion of the whole upper part of area 6a causes only a transient weakness of the contralateral limbs, and that of the entire complex of cytoarchitectonic subareas where face and mouth movements are represented (6a lateral part, 6bα and 6bβ), causes only a modest drooping of the corner of the mouth contralateral to the lesion. The facial deficit is so slight that already at the second day after operation, the affected side can be retracted (Green and Walker, 1938).

Our data on the ablation of the postarcuate premotor area confirm this paucity of the elementary neurological disturbances. They show, however, that a lesion in this area causes a prolonged incapacity to perform some motor acts triggered by visual and somatosensory inputs. The lesion also produces a peculiar hemi-inattention syndrome.

Motor Deficits

The most striking motor deficit we have observed was the animal's incapacity to grasp food with its mouth when it was presented near to the face or even in contact with it on the side contralateral to the lesion. This mouth grasping movement is a rather complex act involving localization of the stimulus, turning of the head, opening of the mouth, contraction of the facial muscles and finally an approaching movement of the mouth towards the stimulus.

An incapacity to perform such a complex act may have three explanations which are not necessarily mutually exclusive. The first is that the disturbance is a consequence of a paresis of the muscles involved in the task. This appears to be rather unlikely. Our monkeys were able to turn their head fast and in an appropriate way when stimuli were presented outside the peribuccal space; they were able to open the mouth for taking food presented centrally or when they were frightened; there were no obvious asymmetries between the two halves of the face at rest or during the expression of emotions. Thus, since the elementary acts necessary for grasping were intact and could be executed in a context other than food grasping, the paresis hypothesis does appear to be improbable.

The second possible explanation is that the motor deficit is a consequence of the neglect. If the animal was not fully aware of the nature and location of the stimulus, it might initiate the movement but be unable to complete it. This explanation is contradicted by the observation that, when the neglect receded and the animal was able to detect the stimulus and to reach for it, the act was still executed in a simplified impoverished way.

The third and most likely possibility is that the deficit consists of an incapacity of programming the motor act using the appropriate visual and somatosensory stimuli. This interpretation stems not only from the difficulty of explaining the disturbance in terms of elementary deficits but also from the properties of the neurons located in this area. Particularly relevant in this respect are the class 3 neurons of the postarcuate cortex (Rizzolatti *et al.*, 1981*a*). These neurons respond very little to passive stimuli but they become active when the animal performs a particular complex motor act (*see* Introduction). Since these neurons do not fire when the animal makes other movements (even with the same muscles), they appear to be the most likely candidates for the units that trigger specific motor acts. The input contingencies for starting the motor program are probably set up by the postarcuate class 1 neurons. These neurons are selective for certain locations of the stimuli in peripersonal space and they prefer certain stimulus sizes and, sometimes, particular directions of movement.

In contrast to the mouth deficits, the motor disturbances in the arm had a less specific character. Essentially they consisted of a reluctance to use the contralateral arm and of a certain clumsiness of finger movements. The preference for the contralateral arm is not surprising given the vast arm and hand representation in the destroyed area; what was rather disappointing was the fact that no specific complex motor act appeared to be impaired. We think that this lack of specific deficits, rather than depending on some different organization principles for arm and mouth movements, is due to a bilateral representation of hand movements in the postarcuate cortex. There are three sets of data that point in this direction. Deuel and Dunlop (1979) described a characteristic incapacity of the monkey to bring food to the mouth with the hands after a bilateral lesion of both banks of the postarcuate cortex. The animals were not paretic after the ablation, yet they reached for food, slowly bringing their mouth to it. This behaviour was not present in animals with a unilateral lesion. As in our experiments these animals showed only a strong preference for the ipsilateral hand. G. Rizzolatti, C. Scandolara and M. Gentilucci (unpublished data) found that in the postarcuate cortex there are neurons that fire concomitantly with active movements of the hand towards the mouth, regardless of which hand the monkey uses. Finally, evidence in favour of an organization of hand-mouth movements by the postarcuate cortex is provided by stimulation experiments. With prolonged stimulation of this cortex, a slow flexion of the hand towards the mouth is typically induced (Ferrier, 1876). Thus it appears that this type of movement is, like the lateral mouth grasping, another complex motor act programmed by the postarcuate cortex. A major difference between the two acts is that the arm movement has a bilateral control.

In conclusion, as far as the motor role of area 6 is concerned, our data clearly support the notion that this area plays a role in organizing complex motor acts. Furthermore they suggest that this area is subdivided into subregions related to specific motor acts. Two of them, lateral mouth grasping and the movement of bringing food to the mouth, appear to be organized in the postarcuate subdivision of area 6. The important findings of Kuypers and his colleagues (Haaxma and Kuypers, 1975; Moll and Kuypers, 1977) that visually guided finger movements and the capacity to reach around a visible object to visible food, both depend on the integrity of area 6, are other examples of area 6 motor programs. Finally the part of area 6 that we studied is clearly responsible for motor programs triggered by external stimuli. This differentiates it from the medial part of area 6 (supplementary motor area) which contains neurons that are poorly responsive to passive stimuli and which probably plays a role in self-generated motor programs (Brinkman and Porter, 1979; Wise and Tanji, 1981).

Attention Deficits

A particularly prominent aspect of the consequences of postarcuate premotor lesions is the presence of attention disturbances. These disturbances consist of a unilateral neglect for the contralateral half of the body, especially the contralateral face, and for peripersonal space. There were no obvious deficits for 'far' space. The hemineglect of a single stimulus was transient, but the presence of an attention bias for the ipsilateral side when two stimuli were presented persisted for the whole period of testing.

Unilateral neglect after frontal lesions typically occurs when area 8 is lesioned (*see* references in Mesulam, 1981). The features of this syndrome are a tendency to deviate the eyes and the head towards the side of the lesion, a poverty of spontaneous eye movements contralateral to the lesion, and a neglect of stimuli in contralateral space. A comparison between this syndrome, replicated in our experiments, and that seen after postarcuate lesions, shows the following differences: (1) tactile deficits are present only if area 6 is involved; (2) visual neglect for 'far' space depends on a lesion of area 8; (3) disturbances of eye movements are related to damage to area 8.

Welch and Stuteville (1958) reported a neglect for tactile and visual modalities after a restricted lesion in the depth of the arcuate sulcus. The neglect was accompanied by a relative poverty of movement of the limbs on the affected side. Welch and Stuteville attributed the deficit to a lesion of a 'facilitatory' cortical zone located in the depth of the arcuate sulcus. Our present data allow us to give another explanation for these findings. A lesion deeply situated in the arcuate sulcus interferes with the activities of neurons of both banks of the sulcus, thus producing a hemi-inattention for far space caused by a frontal eye field lesion, and a tactile and peripersonal neglect due to an area 6 lesion. This interpretation is consistent with the anatomical and physiological data on the organization of the periarcuate region (Pandya and Kuypers, 1969; Jones and Powell, 1970; Chavis and Pandya, 1976; Wurtz and Mohler, 1976; Pigarev *et al.*, 1979; Barbas and Mesulam, 1981; Goldberg and Bushnell, 1981) and permits dismissal of the rather odd concept of a cortical area whose function is exclusively that of facilitating brain structures.

The finding that the neglect assumes different aspects according to the cortical area that is damaged has important theoretical consequences. First, it is not compatible with the idea that a single basic circuit such as the cortico-limbic-reticular pathway proposed by Heilman (Heilman and Watson, 1977; Heilman, 1979) may account for the hemi-inattention. If this idea were correct, the neglect ought to be characterized by similar spatial disturbances regardless of which part of the loop is destroyed. This clearly is not the case as we found that lesions of one area produce neglect of space near the head and lesions of another area produce neglect of space far from the animal.

Secondly, the close relation between the spatial properties of the neglect (far space *vs* peripersonal space) and the type of motor disturbance (eye movements *vs* mouth and arm movements) indicates that areas that organize complex motor acts also have attention functions that are specific for the space in which the movements occur. The recent discovery that in parietal association areas many neurons fire concurrently with certain motor acts (*see* references in Lynch, 1980) is consistent with this concept. Furthermore the fact that in animals a neglect syndrome may occur after a variety of subcortical and cortical lesions (*see* references in Heilman and Watson, 1977; Mesulam, 1981), ranging from the substantia nigra to the superior colliculus and from cortical area 6 to area 7, also supports the idea of a constellation of centres involved in organizing different motor behaviours each of them possessing the capacity to direct attention to the functional space in which the action takes place. This notion of a constellation of centres contrasts with the one in which only a single basic circuit is responsible for selective attention. The electrophysiological evidence in favour of this proposal has been recently reviewed by one of us (Rizzolatti, 1983) and will not be further discussed here.

A final point worthy of emphasis is that external space, although unified to the subject, is represented in the brain by structures that can be affected selectively. Peripersonal space (which in turn can be subdivided into pericutaneous and distant peripersonal space) is closely related to tactile and proprioceptive sensation. This is shown by the presence of neurons responding to somatosensory stimuli and to visual stimuli in the space immediately around the body (Hyvärinen and Poranen, 1974; Leinonen and Nyman, 1977; Rizzolatti *et al.*, 1981*c*) and by the bimodal neglect described in this paper. It is this strict link between personal space and that immediately around the person which led us (Rizzolatti *et al.*, 1981*b*, *c*) to introduce the term peripersonal space instead of the often used 'extrapersonal space' (*see*, for example, Mountcastle *et al.*, 1975). In contrast with peripersonal space, far space has no relation to somatosensory inputs but appears to be strictly linked with oculomotion and, more generally, with contralateral exploratory movements. This is shown particularly well by the properties of the frontal eye field neurons (*see* references in Goldberg and Bushnell, 1981).

The distinction between far space and peripersonal space has rarely been used in neurology. A notable exception is the paper by Brain (1941) on visual disorientation syndromes. In this paper he proposes the existence of a 'grasping distance' and a 'walking distance'. These notions were introduced in order to explain selective disturbances that patients may have for one or the other aspect of space. Particularly interesting in relation to our data is his Case 3, who had difficulty in localizing objects within arm length but not far objects. These data indicate that the distinction between different portions of space that we have found in the monkey also exist in man and it is very likely that disturbances of these different portions of space would be more commonly found with appropriate testing.

ABBREVIATIONS

AM = N. anterior medialis thalami
AV = N. anterior ventralis thalami
Cd = Caudate nucleus
CL = N. centralis lateralis thalami
CM = Centromedian nucleus of thalamus
GP = Globus pallidus
LD = N. lateralis dorsalis thalami
LGNd = Lateral geniculate nucleus
LP = N. lateralis posterior thalami
MD = N. medialis dorsalis thalami
mc = N. medialis dorsalis thalami, pars magnocellularis
pc = N. medialis dorsalis thalami, pars parvicellularis
mf = N. medialis dorsalis thalami, pars multiformis
MGN = Medial geniculate nucleus
NR = Red nucleus

OT = Optic tract
Pf = N. parafascicularis thalami
Pul = N. pulvinar
R = N. reticularis thalami
RE = N. reuniens thalami
Rh = N. rhomboideus thalami
SNc = Substantia nigra, pars compacta
SNr = Substantia nigra, pars reticulata
ST = Subthalamic nucleus
TMT = Mammillothalamic tract
VA = N. ventralis anterior thalami
VAmg = N. ventralis anterior thalami, pars magnocellularis
VI = N. ventralis intermedius thalami
VLc = N. ventralis lateralis, pars caudalis
VLm = N. ventralis lateralis, pars medialis
VLo = N. ventralis lateralis, pars oralis
VPI = N. ventralis posterior inferior thalami
VPL = N. ventralis posterior lateralis thalami
VPM = N. ventralis posterior medialis thalami
ZI = Zona incerta
X = Area X of Olszewski

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ADDENDUM

Following submission of this paper, an article by Halsband and Passingham (1982) appeared dealing with the effect of bilateral lesions of the premotor area in monkeys (*Brain Research, Amsterdam*, **240**, 368–372). Although the extent of the lesions and the methodology of their experiments are different from those that we have employed, the general conclusions of their work are in good agreement with the ideas expressed in this paper.

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THE LONG-TERM EFFECTS OF REMOVAL OF SENSORIMOTOR CORTEX IN INFANT AND ADULT RHESUS MONKEYS

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SUMMARY

A comparison is made between the long-term effects of the unilateral removal of sensorimotor cortex in infant and adult rhesus monkeys. Both infants and adults recovered to a remarkable extent. They walked, climbed and jumped with ease. However, neither infant nor adult monkeys could grip food by using thumb and forefinger independently of the other fingers. It was demonstrated in the adults that there was a permanent impairment in the use not only of the fingers but also the wrist and forearm. The results do not support the claim made by Kennard (1942) that infants recover more completely than adults from the effects of brain lesions. An analysis of the relevant evidence suggests that compensation occurs only when the animal is very immature at the time of operation. The brain is much more mature in a neonatal monkey than a rat or hamster. True compensation can probably only occur in monkeys if the lesion is made well before birth.

INTRODUCTION

There is a belief current in the literature that recovery from the effects of cortical damage is more complete if the lesion is inflicted in infancy rather than adulthood. This belief has as one of its foundations the classical experiments of Kennard (1942) who studied the recovery of infant and adult monkeys after removal of the motor cortex. Her work has been so influential that the phase 'the Kennard Principle' has been used to refer to the claim that early lesions result in less disability (Teuber, 1974).

Kennard (1942) stated that 'in mammals comparable lesions of the cerebral cortex affecting motor status have far less permanent and severe effects when the injury is sustained in infancy than when it occurs in adulthood'. Proper support for such a claim could come only from studies in which the adults were given as long to recover as the infants, and in which the progress of the monkeys was charted for a considerable period of time. The experiments reported by Kennard (1936, 1938, 1940, 1942) do not satisfy these basic requirements. Of the infants that she describes in these papers some were allowed to survive for one or even two years after the operation; yet almost all the adults were killed within a few weeks after surgery.

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In one paper Kennard (1940) does refer to 3 monkeys that were operated on during adolescence and then allowed to survive for a further ten months. In all 3 animals one hemisphere was removed. Kennard compares the progress of these monkeys with that of 4 monkeys that were operated on as infants. She claims that the degree of resistance to passive manipulation was 'moderate' in the adults but only 'slight but definite' in the infants. But only one of the infants had the same lesion as the adults; in the others either the frontal lobe or the motor areas alone were removed.

It is important to distinguish two claims. The first is that in the short term a lesion has a less disruptive effect on the infant than the adult. The second is that the long-term recovery is greater in the infant than the adults. Most of the data presented by Kennard are relevant to the first but not the second of these claims. It is not in dispute that, as Kennard (1942) first noted, infant monkeys are much less disabled in the weeks after operation than are adults. However, it may be wrong to interpret the dramatic recovery of the infants as evidence of neocortical plasticity; it is as likely that it occurs because the neocortex has not yet assumed its adult functions and therefore its contribution is not missed (Goldman, 1974).

This point is well illustrated by the study of Lawrence and Hopkins (1976) who investigated the effects of bilateral section of the pyramidal tract. It was known from previous experiments (Lawrence and Kuypers, 1968) that after this operation adult monkeys are unable to make relatively independent movements of the fingers. But when the pyramidal tract is sectioned in infants a few weeks old their hand and arm movements do not differ appreciably from those of normal infants. However, as the normal infants grow up they develop the ability to move their fingers independently. This process is complete around the age of eight months, and it is not until this age that the direct corticospinal connections from motor cortex are fully formed (Kuypers, 1962). If the monkeys with bilateral section of the pyramids are allowed to grow up they fail to match the progress of normal monkeys, and they remain capable only of grasping items with the whole hand.

The present study reinvestigates the long-term effects of cortical sensorimotor lesions in monkeys. To maximize the chances of recovery and of anatomical reorganization the lesions were made unilaterally. Three studies have demonstrated that in rats an aberrant ipsilateral corticospinal path can develop after removal of either part or the whole of one hemisphere just after birth (Hicks and D'Amato, 1970; Castro, 1975; Leong, 1976). Hicks and D'Amato (1970) also claimed that there was some sparing of function in these animals; the normal pattern of the stride was disrupted in rats in which the operation was performed in adulthood but not in the infants.

The pyramidal decussation is not formed in rats until the day after birth (Castro, 1975; Schreyer and Jones, 1982), whereas in monkeys it is fully formed before birth (Humphrey, 1960). Nonetheless, it is possible that if the sensorimotor cortex is damaged in monkeys unilaterally and early in life, compensatory changes could occur in the corticosubcortical paths ipsilateral to the intact hemisphere. Such changes could allow greater long-term recovery of function in infants than in adults.

It is this possibility that is investigated in this paper and in the accompanying anatomical paper by Sloper *et al.* (1983). This paper gives an account of the behavioural outcome. Data on most of the infant monkeys have already been reported in a preliminary paper (Passingham *et al.*, 1978).

The sensorimotor cortex (Brodmann areas 4, 3, 2, 1) was removed from one hemisphere in 6 monkeys. This lesion removes the majority of the cells contributing fibres to the pyramidal tract (Kuypers, 1960). In 4 monkeys the operation was performed in infancy and in 2 when the animals were around 3 years old. All animals were allowed at least eighteen months to recover before formal testing began.

A comparison was also made with 6 other animals in which part of the sensorimotor cortex was removed in infancy. The lesions were placed either in motor cortex (area 4) or somatosensory cortex (areas 3, 2, 1) or in the regions of motor cortex and somatosensory cortex that represent the leg.

Each monkey was tested for its manual dexterity. After removal of motor cortex (Travis, 1955) or section of the pyramidal tract (Tower, 1940; Lawrence and Kuypers, 1968), adult monkeys are unable to pick up small pieces of food between thumb and forefinger while holding the other fingers out of the way. A sensitive test was devised by Haaxma and Kuypers (1975) in which the monkey must remove a cylindrical pellet of food from a slot by inserting thumb and forefinger. In the present study all monkeys were assessed on a simplified version of this task to see if they were capable of a precision grip.

In watching the monkeys with sensorimotor lesions as they performed on this task it was obvious that their limitations were not confined to the use of the fingers. In the 2 adult animals, therefore, an attempt was made to assess formally the degree to which the animal could make the flexible movements of the wrist and arm that are needed to bring the fingers to any point in space.

METHODS

Subjects

Twelve rhesus monkeys (*Macaca mulatta*) were used.

Surgery

Operations were performed on 10 of the monkeys during infancy when they were between six days and three months old, and on 2 of the monkeys when they were around three years old. The ages at the time of operation are listed in Table 1. For convenience the former are referred to as the 'infants' and the latter as the 'adults', although all were juvenile or adult when studied.

In the infants cortical lesions were made by careful removal of a portion of the pia mater and by aspirating any sulcal tissue from which the pia had not been removed. In the adults the lesions were made by aspiration with a small gauge sucker. All surgery was performed under pentobarbitone sodium (Nembutal) anaesthesia and with aseptic conditions.

All lesions were unilateral and were placed in the left hemisphere. The sites of the lesions in the

TABLE 1 DETAILS OF AGE AT OPERATION, SITE OF LESION AND TIME PERIOD FOR RECOVERY

Animal	*Age at operation*	*Lesion*	*Period operation to training*
SM4	26 days	Area 4+SI	2 years, 1 month
SM5	89 days	Area 4+SI	2 years, 1 month
SM6	23 days	Area 4+SI	1 year, 10 months
SM7	14 days	Area 4+SI	1 year, 9 months
ASM13	3 years (approx.)	Area 4+SI	1 year, 7 months
ASM14	3 years (approx.)	Area 4+SI	1 year, 7 months
M1	7 days	Area 4	2 years, 2 months
M2	72 days	Area 4	2 years, 1 month
M3	10 days	Area 4	2 years, 1 month
S12	7 days	Area SI	1 year, 10 months
LSM9	20 days	Leg area 4+SI	1 year
LSM10	75 days	Leg area 4+SI	9 months

different animals are listed in Table 1. In 4 infants and the 2 adults, area 4 was removed together with the primary somatosensory area (Brodmann, 3, 2, 1). The latter area corresponds to Woolsey's (1958) SI and the combined lesion will therefore be referred to as a lesion of area 4+SI. In 3 animals a lesion was placed in area 4, but in only one of these (M2) was all the tissue representing the hand disrupted (*see* Histology). In 1 animal SI alone was removed, and in the remaining 2 animals only the leg area of area 4+SI was removed.

Histology

The histological processing of these brains is described by Sloper *et al.* (1983).

Figs. 1, 2 and 3 present reconstructions of the lesions and parasagittal sections for 6 of the monkeys. In each case the extent of the lesion was confirmed by examination of the retrograde degeneration in the thalamus. A full description of each lesion is summarized below, so that the reader can properly assess the comparability of the lesions in the infants and adults.

SM4 (fig. 1). The depth and extent of the lesion vary along its mediolateral extent, being greater in the medial two-thirds and becoming less laterally. In the medial two-thirds, above or medial to the lower end of the intraparietal sulcus, the walls of the central sulcus have been completely removed and from the exposed surface of the hemisphere all of area 4 anterior to the sulcus and areas 1 and 2 posterior have gone. Although the anterior margin of the lesion crosses the precentral dimple, no evidence of area 4 cortex remains at this level. The cortex of area 2 in the anterior wall of the intraparietal sulcus has been preserved and is not undercut. Area 5 is intact and the characteristic cytoarchitecture of its anterior part with the large cells in layer V can readily be recognized. Lateral to the tip of the intraparietal sulcus the damage becomes gradually less deep and the deep thirds of the anterior and posterior walls of the central sulcus are preserved. The cortex remaining is that of areas 3a and 3b, and nothing characteristic of area 4 can be seen. The lesion ends just at the lower end of the central sulcus.

SM5 (fig. 1). The entire mediolateral extent of the cortex of areas 4, 3 and 1 on the lateral and medial surfaces of the left hemisphere has been removed, and parts of these areas in the upper wall of the cingulate sulcus have been undercut as the lesion has removed all the underlying white matter and extends up to the deep margin of the cortex. No sign of the central sulcus remains but the damage has not extended deeply, not more than to the junction of the superficial and middle thirds of the intraparietal sulcus posteriorly and of the arcuate sulcus anteriorly. The cortex of area 2 on the exposed lateral surface has been removed and that in the superficial part of the anterior wall of the intraparietal sulcus has been undercut. There may be marginal involvement of area 6 at the level of the bend of the arcuate sulcus. Areas 5 and 7 appear to be intact.

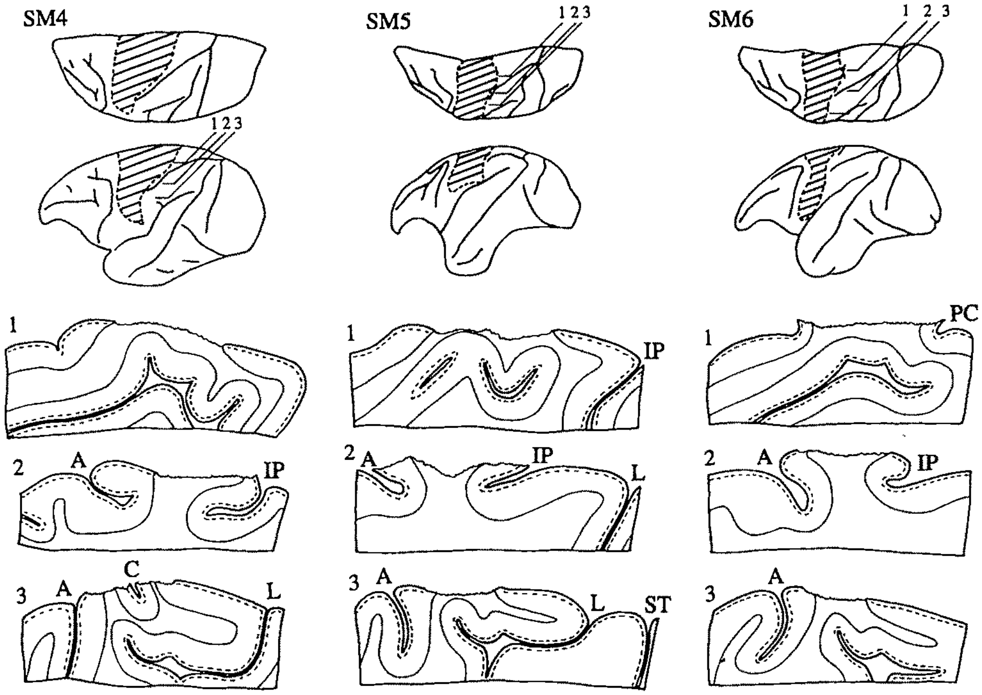

FIG. 1. Dorsal and lateral views of the cortex and parasagittal sections in 3 infants with sensorimotor lesions. The lateral views show the levels at which the sections were taken. A = arcuate sulcus, C = central sulcus, IP = intraparietal sulcus, L = lateral sulcus, ST = superior temporal sulcus.

SM6 (fig. 1). Most of the aims of the operation were achieved. There is no sign of the central sulcus and all of the cortex of areas 4, 3 and 1 has been removed. The cortex of area 6 has probably not been damaged and the posterior wall of the arcuate sulcus has not been undercut. The cortex of area 2 on the lateral surface of the hemisphere has been removed but that portion of it in the posterior wall of the postcentral dimple and in the anterior wall of the intraparietal sulcus is preserved and is not undercut. The cortex of areas 5 and 7 are preserved.

SM7. The extent of the lesion in this brain is so similar to that of SM5 that it does not justify a separate description. The only essential difference seems to be that in addition to the removal of areas 4, 3, 1 and 2 most of area 5 has probably been either removed or undercut.

ASM13 and ASM14 (fig. 2). The lesions in both brains are very similar, the major difference being that in ASM14 the lesion went a little deeper into the white matter and also went closer to the bank of the arcuate sulcus where it bends sharply with the possibility that area 6 may have been marginally damaged. In both animals the cortex of the entire mediolateral extent of areas 4, 3 and 1 has been removed and there is no sign of the central sulcus; where area 2 lies on the exposed lateral surface it has been removed and that part of it in the anterior wall of the intraparietal sulcus has been undercut. It is difficult to be certain about area 5; most of it has probably been preserved but its anterior margin may have been encroached upon. The cortex of areas 4, 3, 1 and 2 on the medial

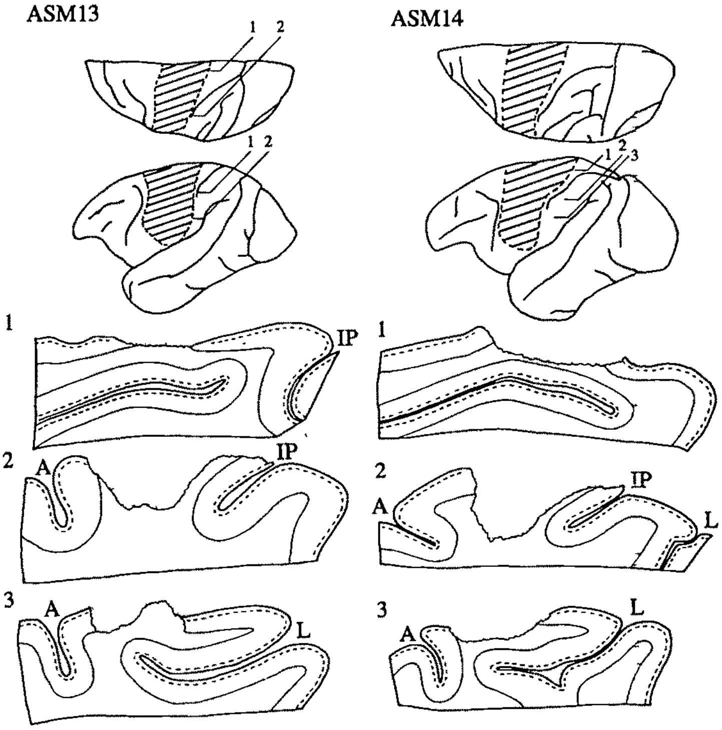

FIG. 2. Dorsal and lateral views of the cortex and parasagittal sections in 2 adults with sensorimotor lesions. Labels for sulci as in fig. 1.

surface of the hemisphere has been removed but parts of these areas in the upper wall of the cingulate sulcus have been preserved, and their connections may be intact as there is a band of white matter deep to them.

M1. This is a narrow strip-like lesion that is confined to area 4 and only affects the cortex on the exposed surface of the precentral gyrus. It is narrowest at the level of the bend of the arcuate sulcus and expands, anteroposteriorly, medial and lateral to this. It just reaches the medial margin of the hemisphere but does not involve the cortex on the medial surface or in the upper wall of the cingulate sulcus. Laterally it ends at the lower end of the central sulcus. The cortex of area 4 in the anterior wall of the central sulcus is quite intact. There is a small deep lesion in the white matter anterior to the central sulcus, but it does not appear to undercut the tissue in the sulcus.

M2 (fig. 3). This lesion removes or undercuts the whole of area 4 and probably also damages the posterior part of area 6. Over the entire mediolateral extent of the precentral gyrus the cortex of area 4 and the posterior part of area 6 has been removed and a deep extension of the lesion into the white matter undercuts the cortex of area 4 and, at certain levels, that of area 3a in the anterior wall and fundus of the central sulcus. The cortex in the upper wall of the cingulate sulcus has also been undercut and that on the medial surface removed. Over most of its mediolateral extent the somatic sensory area in the posterior wall of the central sulcus and on the surface of the postcentral gyrus is intact, but close to the lower end of the central sulcus a deep but narrow extension of the lesion in the white matter extends right around the depths of the central sulcus. It is at the junction of the grey and white matter, extends up to the surface of the postcentral gyrus and clearly undercuts completely the cortex in the anterior and posterior walls of the central sulcus. Thus in this region of the representation of the face,

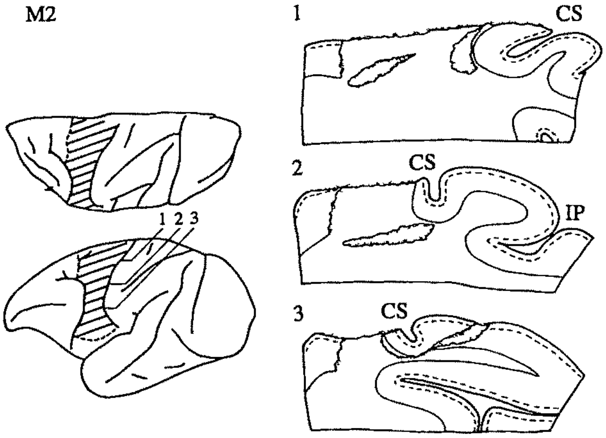

FIG. 3. Dorsal and lateral view of the cortex and parasagittal sections in an infant monkey with a lesion in motor cortex. Labels for sulci as in fig. 1.

both the somatic sensory and motor areas have their connections interrupted. The damage ends at the lower end of the central sulcus.

M3. On the exposed surface of the precentral gyrus all of the cortex of area 4, with the exception of a part of the representation of the leg at the medial margin of the hemisphere, has been removed. The cortex of area 4 in the upper wall of the cingulate sulcus is intact. The depth of the anterior wall of the cingulate sulcus is intact. The depth of the anterior wall of the central sulcus which has either been removed or undercut varies along the mediolateral extent. In the representation of the arm and hand the more superficial part of the anterior wall has been undercut but the deep half at least is preserved. The part of area 4 related to the hand has therefore only been partially damaged: all that on the exposed surface of the hemisphere has been removed but a considerable portion of that in the anterior wall of the central sulcus has been preserved.

Apparatus

The monkeys were trained in a Wisconsin General Testing Apparatus. All monkeys sat in a transport cage for the initial testing of hand preference. On subsequent tests 8 monkeys sat in a transport cage and 4 (SM4, SM5, ASM13, ASM14) in a primate restraining chair. The apparatus required for each of the tests is described in the relevant section below.

Training

No animal was trained until a long period had elapsed after the operation, so as to maximize the chances of spontaneous recovery. Table 1 gives the postoperative period for which each animal was left without training. The shortest periods were for the control animals with lesions of the leg area (LSM9, LSM10). All other animals were left for over eighteen months.

Comparison of Infants and Adults

All animals were assessed on the following 3 tests.

Hand preference. Each animal's hand preference was established by allowing it to reach for food through the bars of the transport cage. In all 140 trials were given, 40 trials a day. A peanut was presented on 100 trials and a larger pellet of monkey chow on 40 trials.

An attempt was then made to force all animals to use the right arm, that is, the affected limb. This was done by replacing the front grill of the transport cage with a perspex screen in which there were two holes, one on the left and one on the right. The holes were positioned such that food presented on the monkey's right could only be reached by putting the right arm through the appropriate hole; in the same way food on the left could only be secured with the left hand.

Some animals still refused to use their right arm. These animals were then trained in a restraining chair. The experimenter held the left arm while encouraging the animal to pick up fruit or pellets of chow with its right. Since the animals still failed to reach with the affected limb they were then reminded of the use of the arm. The experimenter repeatedly moved the animal's arm passively onto the food. This procedure proved effective (*see* Results).

Holes. The animals were required to pick peanuts out of circular holes. The holes were set in square black perspex plaques (7.5 cm by 7.5 cm) fixed to a horizontal testing board (67 cm long; 26 cm wide). The holes were 6, 5, 4, 3 and 2 cm in diameter. The animal was first presented with the 6 cm hole. If it succeeded in removing the peanut on 5 successive trials it was then presented with the hole 1 cm smaller in diameter. If it failed to remove the peanut on one trial it was then retested on the hole 1 cm larger. Testing was stopped when the animal had succeeded on 5 successive trials on the smallest hole or had failed on 10 successive trials on any other hole. The choice of hand was forced by making the animal reach through one of the two openings in the perspex screen. The left hand was tested first and then the right.

Slots. The animals were required to pick cylindrical pellets of monkey chow or apple (15 mm diameter, 12 mm depth) out of slots. The slots were set in square black perspex plaques (7.5 cm by 7.5 cm) fixed to a horizontal testing board. Each slot had a central well (15 mm in diameter) to hold the pellet and 2 grooves (7 mm wide, 21 mm long, 12 mm deep) leading into the well from either side. The pellet was flush with the top of the perspex, and thus it could be picked up only by inserting the fingers into the grooves.

The rim of the groove was marked with a white line to make the orientation of the groove obvious. Four plaques were used which differed in the orientation of the slot. As the animal looked down on them the 4 orientations were (1) | (2) \ (3) — (4) /. The animals were presented with the slots in this order starting with the easiest orientation, No. 1. They were moved to the next in the series when they succeeded on 5 successive trials on any particular orientation. If they failed on any trial with orientations 2, 3 or 4 they were put back on orientation 1.

Further Testing of Adults

To succeed on the slot task the monkey must be able to grasp the pellet between thumb and forefinger. But it must also turn its wrist so as to approach the slot from the angle appropriate to the orientation of the line. It was noted that the animals with sensorimotor lesions used a crude whole hand grasp and failed to reorientate their hands; and this was true also of 2 of the animals in which lesions had been placed in the motor cortex (M1 and M2). It was therefore decided to examine the use of the wrist and arm further after removal of sensorimotor cortex. Four additional tests were therefore devised and these were administered to the 2 adult animals with lesions of area 4+SL.

On all tasks they had only to knock a piece of food (raisin or chocolate bean) off a ledge, although the way that they were to do this differed on the various tests. The food fell onto a metal tray (width 21 cm, length 16 cm, tilted at an angle of roughly 30 deg). The monkey was then able to retrieve the food with its left hand from the bottom of the tray.

The tray was mounted in a three-sided metal box (length 21 cm, width 14 cm, depth 10 cm). The front of the box was open, but it supported a vertical groove at each side into which sheets of clear perspex could be inserted so as to form the front wall. The monkeys had to knock the food off ledges by inserting their fingers, wrist or arm through holes in the perspex (fig. 4). The following sections describe the ways in which they were to do this.

Use of fingers. A piece of food was placed in the centre of a metal ledge (length 21 cm, width 12 cm) which was mounted across the box 1 cm behind the perspex sheet (fig. 4A). The food could be reached through a hole in the perspex sheet and thus knocked off the ledge. The hole in the perspex sheet could be 7.5 cm, 5.0 cm, 2.5 cm, 1.3 cm, or 0.9 cm in diameter. The monkeys started on the largest hole

(7.5 cm) and were tested with successively smaller holes until they either failed to dislodge the food 5 times in a row or refused to continue. If they failed on 5 successive trials on a hole of any particular size they were then tested on a larger hole, one step up in the series. The hole 2.5 cm in diameter was large enough to allow the monkey to insert two fingers at once, but on the smaller holes the monkey could only reach the food by inserting a single finger and holding the other fingers out of the way.

On this and on other tests the left hand was tested before the right. The experimenter indicated to the monkey which hand it was to use by holding the incorrect hand for the first few trials of a session.

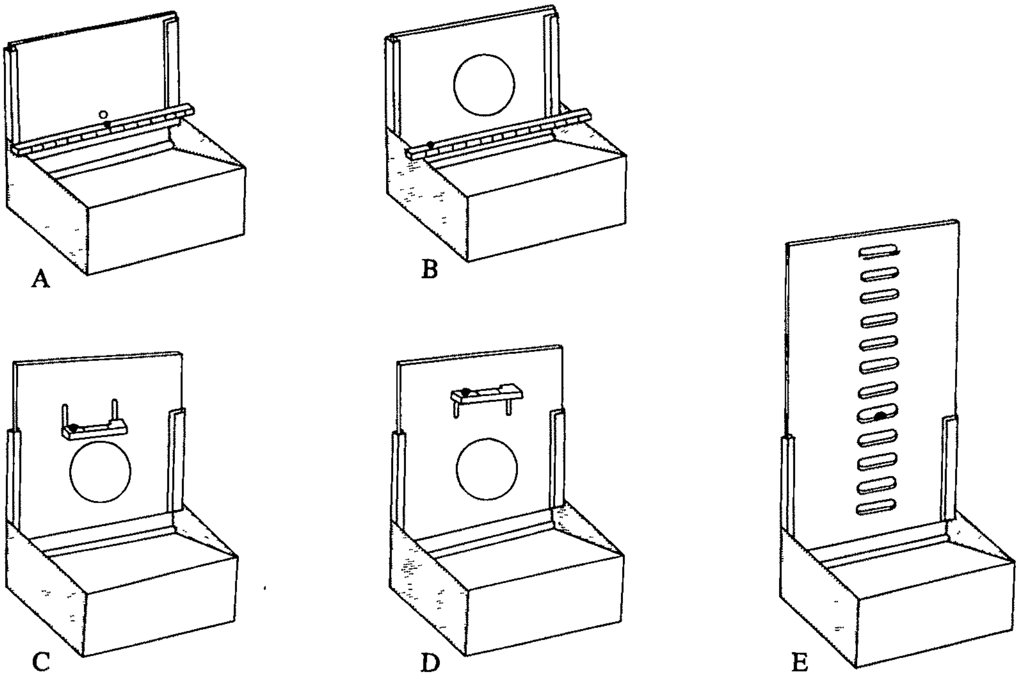

FIG. 4. Apparatus used for testing the use of fingers, wrist and forearm. The monkey sat on the far side of the apparatus and reached through the hole for food. The food is shown as a black ball. A description of the apparatus and of each of the tasks (A, B, C, D, E) is given in the text.

Use of wrist. The monkeys were required to dislodge the food by knocking it with their hand. They inserted their hand through the largest hole used in the previous test, 7.5 cm in diameter. The ledge was placed at one of 4 positions behind the perspex sheet, either immediately behind or 2.5 cm, 5.0 cm or 7.5 cm behind (fig. 4B). The food was placed at 1 of 14 positions on the ledge from left to right, 2 central positions and 6 to either side. The food could therefore be placed in one of 56 locations in a two-dimensional space behind the perspex. The monkeys were tested first with the ledge immediately behind the perspex and then 2.5 cm, 5.0 cm and 7.5 cm back in turn. For each of these 4 distances the raisin was placed in each of the positions to the right and to the left in turn. This was done by starting with a central position and then moving it successively to the right; and then starting again in a central position and moving it successively to the left. If the monkey failed to reach the food in one position it was tested again on the last position on which it had succeeded and then retested on the position at which it had failed. If the monkey failed 3 times at one position it was judged to be unable to reach it. For each of the 4 positions of the ledge the left hand was tested before the right.

The central 6 positions along the ledge could be reached directly through the hole without turning the wrist, but the lateral 4 positions on either side could be reached only with some deviation of the wrist. The most difficult positions were those to the left for the left hand and to the right for the right hand, since these required a marked abduction of the wrist.

Supination. The monkeys were required to reach through the largest hole, 7.5 cm in diameter. Above the hole and behind the perspex there was a ledge, which could either be level with the top of the hole or 3 cm above it (fig. 4C, D). The food could be placed at 3 positions on the ledge, at the left, right and centre. The apparatus could be positioned at each of 7 distances from the animal, in steps of 2.5 cm.

The monkey could dislodge the raisin by reaching through the hole and then flexing the wrist, but it could only succeed in hitting the food if it supinated the arm. The monkeys were tested first with the ledge in the lower position and then in the higher. For the higher position the monkeys were required to supinate the arm to a greater degree. The food was placed successively in the left, centre and right positions. The most difficult position was to the left for the left hand and to the right for the right hand, since these required the greatest degree of supination. The task was easiest for the middle distances since the monkeys could reach the food without turning their palm right over. The monkeys were tested at each of the distances in turn, starting with the nearest position. The monkeys were said to have failed at any position if they were unable to dislodge the food on 3 trials.

Reaching. It was noticed on the previous test that the monkeys reached less far with their right than their left hand. Their reach was therefore formally tested. A perspex sheet was used which had 12 ledges arranged vertically 2.5 cm apart as a ladder (fig. 4E). The apparatus was positioned at one of 7 distances from the animal in steps of 2.5 cm. The monkeys were tested at each distance in turn, starting with the nearest. The food was placed on each of the ledges in turn. If the animal succeeded at any height it was then given the next one up. If the animal failed at any position it was then retested on the next one down. An animal was said to have failed at any position if it was unable to dislodge the food or refused to attempt to reach it on 5 trials. The left hand was tested before the right.

The monkeys' reach was also tested on the flat. The food was placed ahead of the animal at one of 10 distances in steps of 2.5 cm.

RESULTS

Comparison of Recovery in Infants and Adults

Hand preference. On the test of hand preference all but 2 animals used their left hand on all 140 trials, that is the hand ipsilateral to the cortical lesion. The exceptions were the 2 monkeys with damage to the leg region of area 4 + SI alone: LSM9 used the right hand on all trials, and LSM10 picked up peanuts with the right hand on 55 out of 100 trials and chow pellets on 20 out of 40 trials.

Five animals failed to use their right hand at all when presented with food which could be reached only through the right hand hole in the perspex screen. Three were infants (SM4, SM5, SM6) and the other 2 were the adults (ASM13 and ASM14). One of these monkeys, SM6, was trained to use the right arm by placing large pieces of fruit in the right hand, but for the others this was not possible.

It turned out to be surprisingly easy to retrain these monkeys to use the affected arm, even though for the many months since the operation they had not spontaneously used the arm for any purpose other than locomotion in their home cage. Even in the testing box the monkeys could not be tempted into trying this arm even though the left arm was restrained and the bait was fruit. However, the technique of passively moving the arm on to the food proved highly effective; it took only a few days to persuade the animals of the use of their arm (three days for SM6, six days for ASM14, seven days for SM4). Thereafter all animals would reach with their right arm when necessary during testing, though they almost always transferred the food to their left hand to put it to their mouth. But they were not observed to use the right hand in their home cage even when holding large items of food which monkeys normally hold in both hands.

Holes. With the left hand all animals could easily pick peanuts out of the smallest diameter hole (2 cm). Table 2 shows the smallest hole from which they could remove food with their right hand. There was no difference in performance between adult and infant monkeys. The adult ASM13 and ASM14 were no worse than the infant SM4, SM5 and SM6. Only one of the four infant monkeys with removal of area 4+SI could manage the 2 cm hole and then only occasionally. The exception was SM7 which was also the only one of these animals spontaneously to use its right arm without training.

All monkeys with lesions that did not encroach on the hand area of motor cortex were able to manage the 2 cm hole without difficulty. The one monkey with a complete lesion of area 4 (M2) was able to pick peanuts from the smallest hole at first, but as training continued the animal's performance deteriorated.

This test is a crude one since no measure was taken of the degree to which the animal was adept in retrieving the food. The only monkeys that actually picked the peanut up in thumb and forefinger when using the right hand were animals in which the arm region of area 4 had been partly or wholly spared, M3, S12, LSM9 and LSM10 (*see* Table 2). The other animals were all less skilled with the affected than with the normal hand; they clawed the food out of the smaller holes by pulling it with

TABLE 2. PERFORMANCE OF MONKEYS ON HOLE TASK

Lesion	*Animal*	*Size hole (cm)**	*Precision grip***
Infant 4+SI	SM4	3	—
	SM5	3	—
	SM6	3	—
	SM7	2 (very occasionally)	—
Adult 4+SI	ASM13	3	—
	ASM14	3	—
Area 4	M1	2	—
	M2	2	—
	M3	2	+
SI	S12	2	+
Leg area 4+SI	LSM9	2	+
	LSM10	2	+

*Numbers give the smallest size of hole (cm) from which the animal could pick food.

** — = failure to grip food between thumb and forefinger; + = able to grip food in this way.

several fingers at once. The monkeys with lesions of area 4+SI were particularly clumsy, probably as the result of sensory loss. They often made several attempts at the food when it lay in one of the smaller holes and sometimes dropped it when they had succeeded in getting it out. The 2 adults were not noticeably more clumsy than the infants.

Slots. All monkeys could use the left thumb and forefinger to remove the pellet of food from the slot in any of the four orientations (fig. 5A). No animal with a lesion that included the whole of the hand area of motor cortex could pick up the food from any slot with the right hand (Table 3).

If the pellet was not tight fitting the animals could 'cheat' by raking it out of the slot. This was only possible, however, if the slot was oriented towards the monkey (orientation **|**) or was angled so that the fingers of the right hand could pull along the length of the slot without bending the wrist (orientation \). All monkeys with a lesion that included the hand area of motor cortex could sometimes tug the food out

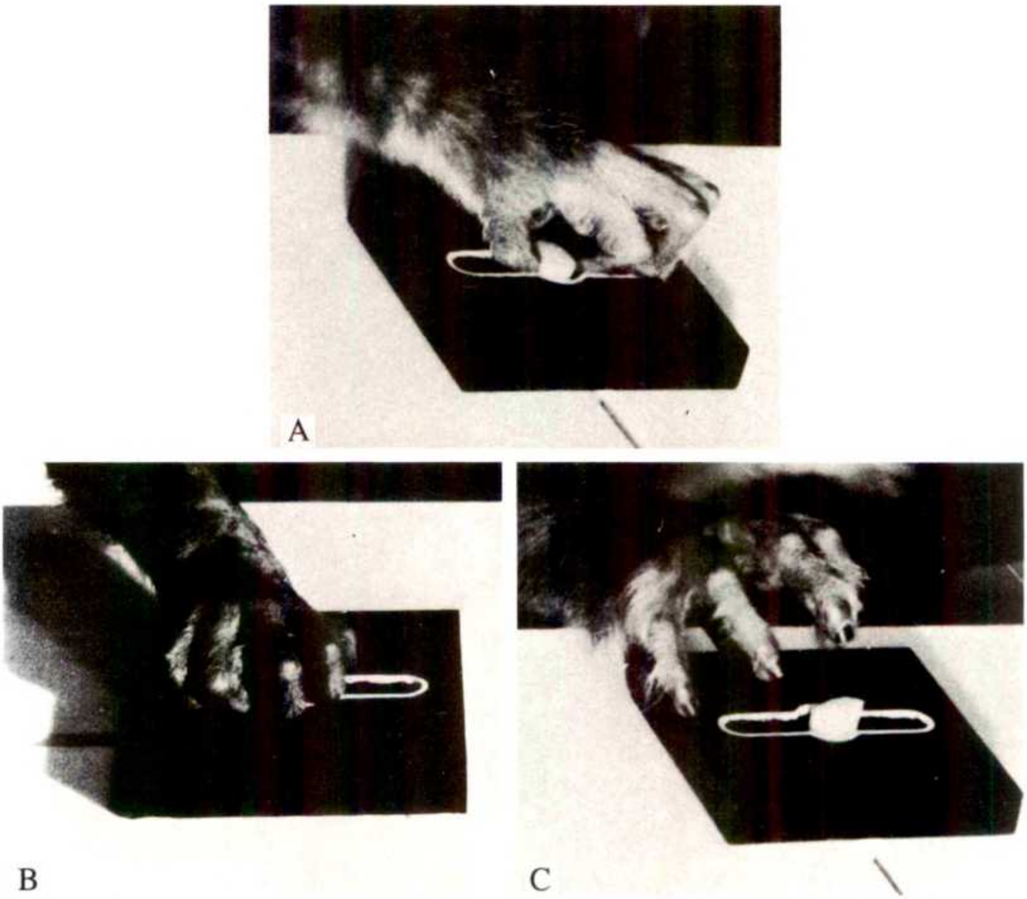

FIG. 5. Monkeys trying to remove food from the slot. A, adult monkey succeeding with left hand; B, infant monkey failing with right hand; C, adult monkey failing with right hand.

TABLE 3. PERFORMANCE OF THE MONKEYS IN TRYING TO PICK FOOD OUT OF A SLOT AT EACH OF 4 ORIENTATIONS

		Orientation of slot			
Lesion	*Animal*	|	\\	—	/
Infant 4+SI	SM4	P	—	—	—
	SM5	P	—	—	—
	SM6	P	—	—	—
	SM7	P	P	—	—
Adult 4+SI	ASM13	P	—	—	—
	ASM14	P	P	—	—
Area 4	M1	P	P	—	—
	M2	P	—	—	—
	M3	+	+	+	+
SI	S12	+	+	+	+

P = animal succeeded in getting the food out, but managed by pulling and clawing at it rather than picking it out; — = failed; + = succeeded.

in the first orientation. Monkeys M1, SM7 and ASM14 could occasionally manage the second (Table 3). Monkey M2 succeeded at first when the slot pointed towards it, but was later unable even to pull the food out in this simple situation. It was not possible to 'cheat' on the other two orientations (/ and —) which demanded movement at the wrist and a pincer grip between thumb and forefinger (fig. 5A). None of the animals with a lesion that included the hand area of motor cortex could remove the food (Table 3).

No difference was observed between infants and adults in their performance on this test. In each case the hand was used in a stereotyped way and an attempt was made to grasp the food by closing all fingers at once. This crude grip is illustrated in the photographs of the right hands of an infant (fig. 5B) and adult (fig. 5C). It can be seen that there was little movement at the wrist.

Other observations. The infants and adults with lesions of area 4+SI did not differ in any obvious way in their general motor status. They were examined while they sat in a primate restraining chair. There was evidence of muscle wasting in the upper arm and forearm of the affected limb. None of the animals used this arm after the operation until persuaded to do so when training began. These monkeys were also less sensitive to pin prick on the right side of the body.

An attempt was made to rate the animals for spasticity as judged by resistance to passive movement. Spasticity was detected in the limbs of infant and adult monkeys with lesions of area 4+SI. These ratings were made by two of the authors, R.E.P. and V.H.P., and by a physiologist, Dr C. Franzini (University of Bologna). The ratings proved unreliable for three reasons: (1) the different raters did not always agree; (2) the ratings for an animal differed at different times; (3) some animals struggled more than others. The basic problem is that the ratings were much affected by the degree to which the monkey was relaxed. Despite repeated attempts to form a sound judgement of the degree of spasticity we were not able to convince ourselves that the infants and adults could be reliably differentiated on this measure. A proper estimate of spasticity could only be made if the monkeys were taught to relax their muscles, using methods such as those of Fetz and Finocchio (1971).

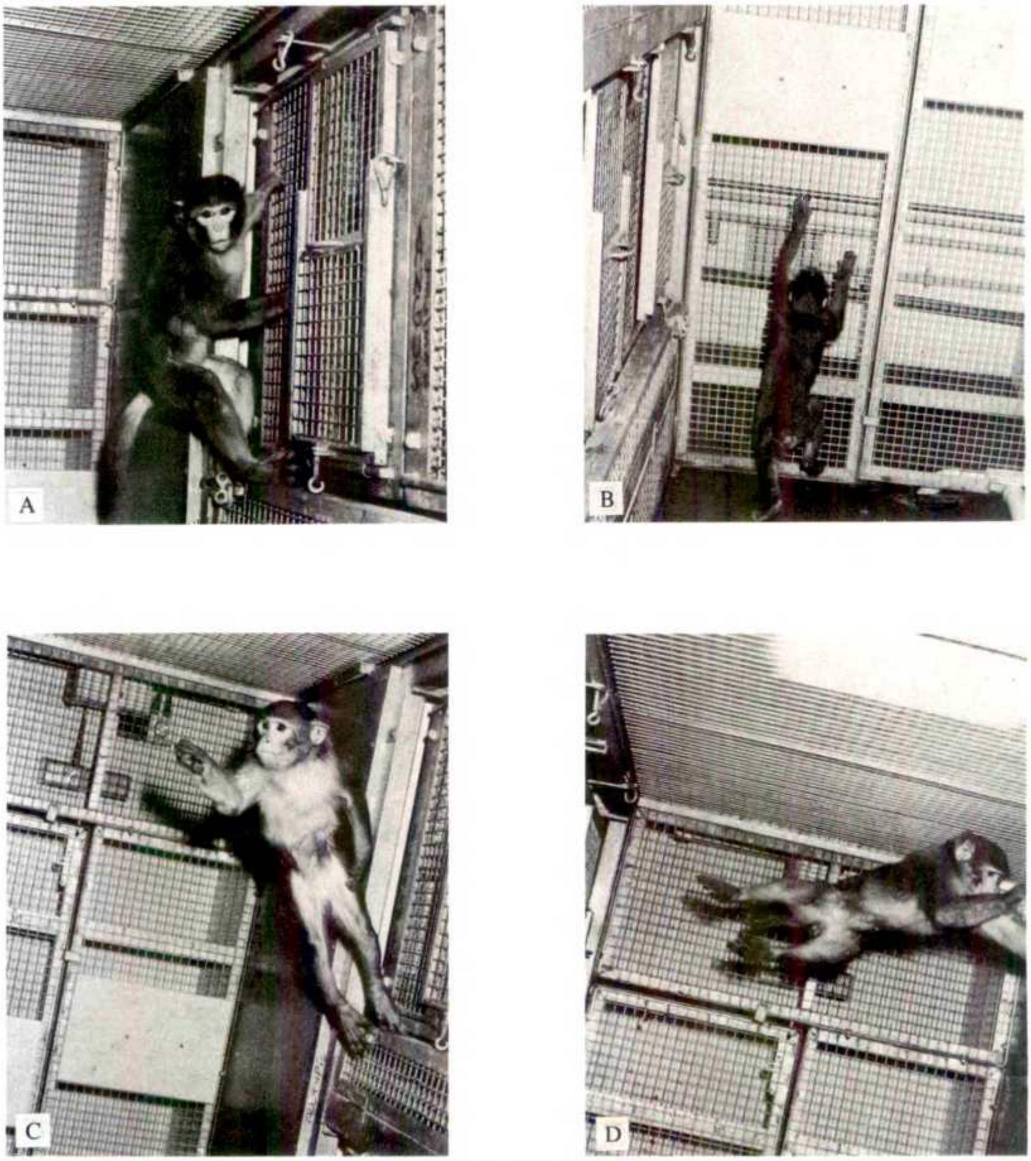

FIG. 6. Adult monkeys moving about the enclosure. A, clinging to a vertical surface; B, climbing the wall; C, jumping off from one wall; D, about to land on the opposite wall.

The animals were also observed while running about a large enclosure (404 cm long, 230 cm high, 107 cm wide). They were encouraged to climb up the mesh walls and to jump from one side of the enclosure to the other, a distance of 106 cm. All monkeys could cling without difficulty to the mesh walls and support their weight (fig. 6A). All could climb (fig. 6B), jump off (fig. 6C) and land safely (fig. 6D). Even at a time when they had not yet started to use their right arm for reaching for food the monkeys with lesions of area 4+SI walked on all fours, and they would actively stretch out the right arm when climbing or leaping (fig. 6D). These monkeys tired easily, which suggests that they may not have been moving efficiently. But in general their movements were remarkably normal. There was no indication that the infants with this lesion had recovered more completely than the adults.

Further Analysis of Impairment in Adults

The remaining four tasks were given only to the 2 adult monkeys (ASM13 and ASM14).

Use of fingers. Neither monkey had any trouble in dislodging the food through any of the 5 holes with their left hand. They could easily poke a single finger through the smallest hole. With the right hand the monkeys could dislodge the food through the hole 2.5 cm in diameter by pressing all fingers onto the perspex such that two fingers entered the hole. When presented with the holes 1.3 cm or 0.9 cm in diameter they simply hit the perspex with all fingers spread out. They were unable to push one finger forwards while holding the others out of the way.

Use of wrist. Fig. 7 shows the 56 positions in which the food could be placed on this test. If the position is not marked this indicates that the monkey succeeded at this position; if it is filled the monkey failed. Both monkeys could reach all positions with their left hand. Both monkeys failed positions to the right of the hole when using their right hand (fig. 7). To reach these positions the wrist had to deviate laterally. Monkey ASM14 also failed two positions to the left. Because the right arm was naturally held at an angle to the hole it was easier to reach the positions on the left without abducting the wrist.

Supination. Fig. 8 shows the 48 positions in which the raisin could be placed on this test. If the square is empty this indicates that the monkey succeeded at that position; if it is filled the monkey failed. Both monkeys succeeded at all positions with their left hand. Monkey ASM14 could not be induced to try any of the positions with its right hand in one month's training. It is possible that it was unable to supinate at all, but we are not confident in this conclusion because we did not try to retrain this arm by lengthy shaping procedures in which the animal is rewarded for successive approximations. Monkey ASM13 was able to supinate to some degree. However it was unable to reach the food if it was placed very near or far and it could not even reach all positions at the middle distance if the ledge was in the upper position (fig. 8). It succeeded where it could dislodge the food without fully turning its hand over. When the apparatus was close the

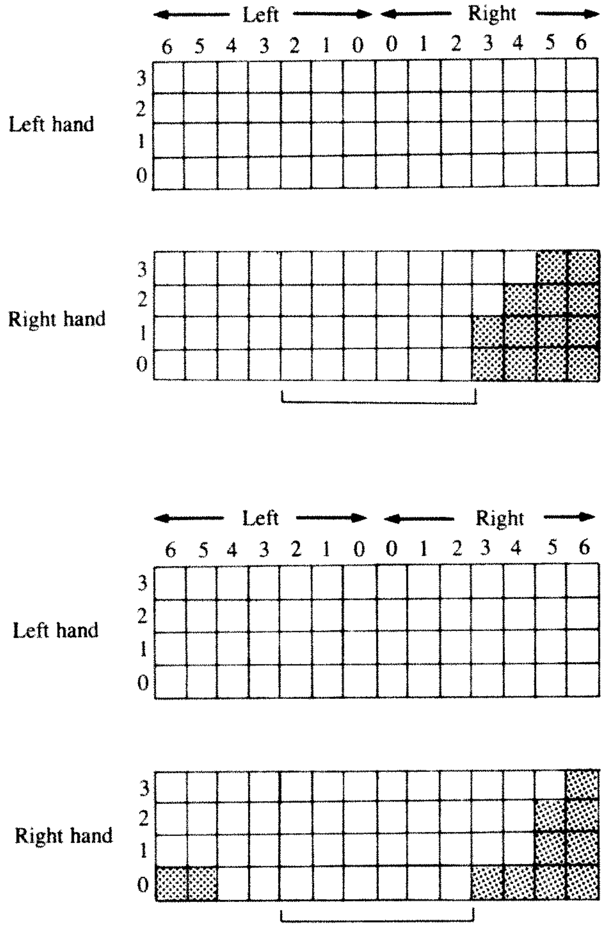

FIG. 7. Grid of positions in which food was placed to test the use of the wrist. The positions are seen from above. The figures on the left give the four distances from the monkey, position 0 being the closest. The positions to the left or right are shown along the top, position 0 being at the centre. The location of the hole through which the monkeys reached is shown at the bottom. If a square is empty the monkey could reach food at that position; if it is filled the monkey failed at that position. The top two grids present the data for the left and right hand of monkey ASM13 and the bottom two grids the data for the left and right hands of monkey ASM14.

monkey failed to supinate at all, reaching through the hole without rotating the arm.

Reach. Table 4 gives the ledges which the monkeys could reach, the lowest ledge being numbered 0 and the highest ledge 12. At most distances the monkeys could reach higher up with their left than their right arm. The monkeys were also able to reach 2.5 cm further along the flat with their left than their right hand. Yet when the arms were passively stretched out by the examiners they reached the same distance.

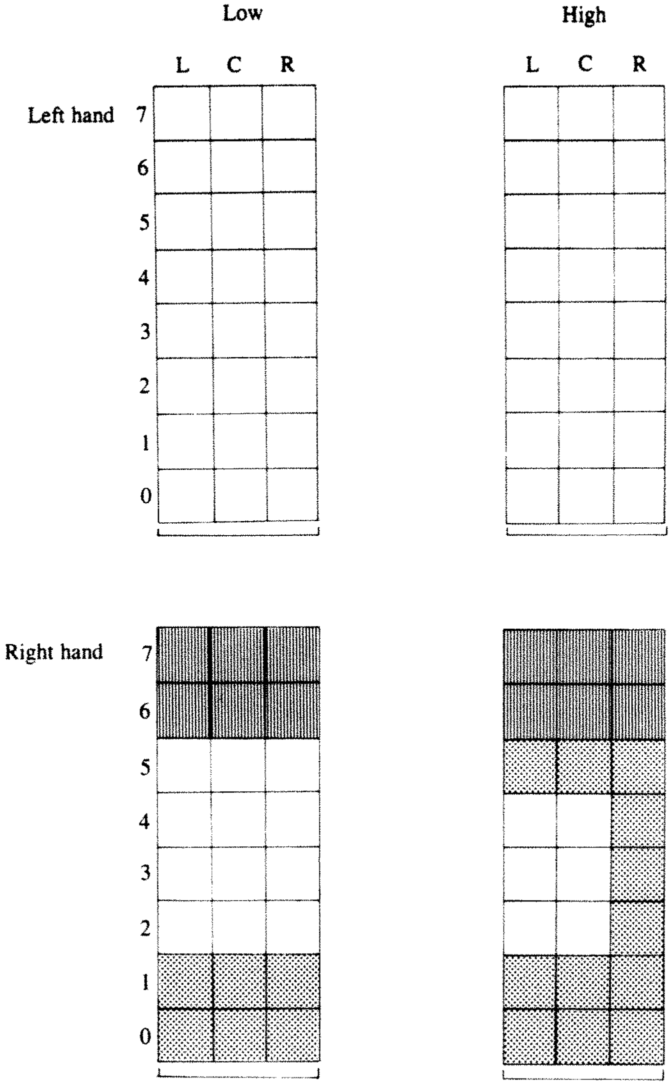

FIG. 8. Grid of positions in which food was placed to test the ability to supinate. The figures to the left give the distances from the monkey. R = right, C = centre, L = left. The grids are shown separately for the low and high positions of the shelf. If a square is empty the monkey could reach food at that position; if it is filled the monkey failed at that position. The monkey could not reach the far positions (marked with lines) with the right hand. Only the data for monkey ASM13 are presented.

DISCUSSION

Recovery in Infants and Adults

This study has produced no evidence that in monkeys the effects of lesions of sensorimotor cortex are less severe or long lasting if the damage is incurred in infancy. After operation early in life the monkeys with damage that included the hand area of motor cortex never developed the precision grip with their fingers. After operation in adulthood the monkeys recovered their general motor abilities to a remarkable degree given time. When observed over eighteen months after the operation the infant and adult monkeys were not distinguishable in their locomotion or manual skill as assessed on simple tests.

TABLE 4. THE HEIGHT THAT THE MONKEYS COULD REACH AT EACH OF 6 DISTANCES

Animal	*Distance*	*Left hand**	*Right hand**
ASM13	0	8	7
	1	8	7
	2	8	6
	3	8	6
	4	7	5
	5	6	4
	6	5	5
ASM14	0	9	8
	1	7	7
	2	8	7
	3	6	6
	4	5	5
	5	5	4
	6	—	—

* The figures indicate the highest ledge the animal could reach. The lowest ledge was numbered 0.
— = failed at all heights at that distance.

These findings do not contradict any of the actual experimental results reported by Kennard, although they provide no support for her general conclusions (Kennard, 1942). Kennard (1940) stated that after a unilateral removal of area 4 in infancy a monkey fails to develop 'fine prehensile movements of the distal portions of the extremities'. As has been pointed out in the Introduction she never directly compared the long term outcome for infant and adult monkeys after damage to sensorimotor cortex alone. She stated (Kennard, 1940) that spasticity is more marked after removal of one hemisphere in adulthood rather than infancy. But in the present study it was not found possible to measure spasticity with any degree of accuracy. One may be sceptical about Kennard's assessment and particularly so when she claims only a slight difference between monkeys.

It would appear that Kennard based her conclusions on two facts: (1) infants recover quickly from surgery and grow up to be remarkably normal in many respects; (2) adults are severely paralysed for the weeks after surgery. Yet she recognized the reason for the lack of a severe paresis in the infants, arguing that early in life 'motor performance is evidently largely subcortical' (Kennard, 1938). Thus a defect in fine prehension can only become evident at a time at which the cortex is mature enough to direct relatively independent finger movements (Lawrence and Hopkins, 1976).

Kennard never supplied the third piece of evidence that she needed, that is, the long term outcome in the case of adults. In her first paper (Kennard, 1936) she described 10 adolescent or adult macaques in which the left motor and premotor areas were first removed and then the same areas were removed on the right side at a second operation between four days and three months later. She does not say for how long the animals were examined after the second operation, although it is clear from the text that at least some of them survived for no more than six weeks. The only infant cited with a comparable lesion had its first operation at 10 days and its second at 5 months; this animal was allowed to survive for at least eighteen months after the second operation. Kennard (1936) claims that 'the degree of ultimate recovery' was greater in the young animal, but provides no data on which the reader can assess the ultimate recovery of the adults.

Descriptions were given of a further 6 monkeys in a later paper on reorganization of function in infancy (Kennard, 1938). In 5 animals motor cortex was removed bilaterally in two stages when they were infants; the lesions differed in the extent to which additional frontal and parietal areas were damaged. In the sixth animal motor and premotor cortex were removed from the left hemisphere during the fourth week of life, and a right hemispherectomy was performed when the animal was 18 months old. The disability was said to be 'more extreme than in any other animal in this series following any lesion'. But only one other animal had a comparable lesion, and the older monkey was allowed to survive for only six weeks after surgery.

A final paper (Kennard, 1942) gave a Table in which information summarized for 16 monkeys with bilateral motor and premotor lesions. Unfortunately here, as elsewhere, it is not always possible to identify those animals that have already been mentioned in previous papers. The Table briefly describes the extent of the recovery in the first week and the first month, and also rates the degree of spasticity. But the 11 monkeys with late lesions were killed between eight and twenty-eight days after operation; whereas 4 of the 5 monkeys with early lesions survived for much longer, one year in one case and two years in the other 3.

In the present study the long term outcome is charted for 2 monkeys in which sensorimotor cortex was removed in adulthood. There was no indication that the adults recovered to a lesser degree than the infants. It is, of course, possible that more subtle and detailed tests might reveal a difference missed by the relatively crude measures used here. No attempt was made to assess the strength of the affected limbs, although it is known that after removal of the hand area of motor cortex (Black *et al.*, 1975) or section of the pyramidal tract (Beck and Chambers, 1970), the forelimb is much weaker. Nor was any assessment made of the speed with which the monkeys could react. Several studies have reported that after section of the pyramidal tract, monkeys are slow to respond. Hepp-Reymond and colleagues (1970, 1972) taught monkeys to press a thin transducer between thumb and forefinger; after the operation the monkeys were slow to exert full force. Under some conditions the monkeys are slow to choose which of two keys to press, although their reaction time is normal when they are required simply to press a single key (Beck and Chambers, 1970). Laursen (1977) has also shown that the monkeys are slow to make repetitive movements, as in the repeated tapping of a lever. Comparisons have still to be made between infants and adults with cortical lesions using measures such as these.

Even if it were accepted that spontaneous recovery is no greater in infants than adults it could still be argued that the infants might benefit more fully than adults if therapeutic measures were applied. We know that after removal of the hand and arm area of motor cortex, monkeys recover their strength more quickly if they are forced to exercise the affected limb by pulling against weights (Black *et al.*, 1975).

Two other studies have investigated the extent to which training can help to restore the ability to make fine movements of the fingers. Chapman and Wiesendanger (1982) have reported that after section of the pyramidal tract on one side, 3 monkeys were able to recover their skill in removing pieces of food from holes in a board after extensive postoperative training. But the task did not require the monkeys to flex thumb and forefinger independently of the other fingers. Furthermore the lesions were not complete.

Hepp-Reymond and colleagues (1970, 1972) have investigated the value of extensive preoperative training. Before operation the monkeys were trained to press a thin wafer, and it is reported that they can continue to do this when tested after section of the pyramidal tract. The degree to which postoperative training can help, however, should not be exaggerated. There was no requirement that the monkeys press the wafer by flexing only thumb and forefinger. It has still to be shown that the full range of independent finger movements can be restored with sufficient training before surgery.

Only one therapeutic measure was applied in the present study. It was essential to test the abilities of the affected limbs, but 2 of the infants and both of the adults at first refused to reach out for food with their right hand, even though large baits were used to tempt them to do so. These monkeys had not used their right hand to feed themselves in the many months since operation. Yet it turned out that they could be induced to use it again after only a few days of therapy in which the hand was passively guided on to food by the experimenter. The value of training by passive movements as a therapy for paralysis has been noted by Brodal (1973), who comments that it draws attention to the way in which the movement is to be executed and thus assists in the voluntary production of the required movement. In the present study all monkeys used all four limbs when walking and climbing; but it was as if some of them needed to be reminded of the use of their right arm as a means for retrieving objects. The training was as effective in adults as in infants.

The present study has not explored all possible tests and training procedures. But it is fair to suggest that the burden of proof now lies with those who wish to maintain that after removal of sensorimotor cortex adult monkeys are more permanently disabled than infants.

Extent of Recovery

All animals made a remarkable recovery. When allowed to roam about freely in a large enclosure they walked, climbed and jumped with impressive ease. However, their apparent facility when walking may be deceptive, and for three reasons. First, they had the normal use of the left side of their body. Secondly, the undamaged hemisphere had some control of the proximal musculature of the affected side (Brinkman and Kuypers, 1973). Finally, the animals could 'cheat', that is, they could achieve the same end in novel ways, thus avoiding the necessity of attempting the movements of which the right limbs were no longer capable.

Both infant and adult monkeys with lesions in area 4+SI were able to remove food from a hole of 3 cm in diameter or from a slot that was orientated towards them. However, none of them was as skilled as the 2 control animals with lesions of the leg area of 4+SI. Abnormalities in the use of the fingers have been previously reported in monkeys after removal of motor cortex (Kennard, 1942; Travis, 1955) or section of the pyramidal tract (Tower, 1940; Lawrence and Kuypers, 1968; Lawrence and Hopkins, 1976).

Neither of these tasks required the animals to use thumb and forefinger independently of the other fingers or to bend the wrist. However, if the slot was in the orientation — the food could only be picked out if the monkey turned the wrist so as to allow thumb and forefinger to enter the slot (*see* fig. 5). Neither infant nor adult monkeys with lesions in area 4+SI ever succeeded in removing the food under these conditions. They never recovered the normal use of wrist and fingers.

Of the infant monkeys with lesions in area 4 alone only one, M2, had a complete lesion; and this animal also failed to pick food out from the slot when it was orientated in this way. Monkey M1 also failed, but monkey M3 succeeded. It is not clear why this was so, since in both monkeys tissue had been removed on the lateral surface but much or all of the tissue in the anterior bank of the central sulcus was spared. Studies of the effects of microstimulation of motor cortex indicate that much of the tissue controlling movements of the wrist lies on the lateral surface (Kwan *et al.*, 1978; Sessle and Wiesendanger, 1982). Abnormalities in the use of the wrist might therefore be expected after removal of this part of the motor cortex. But this does not explain the apparent lack of impairment in monkey M3.

Microstimulation at different sites within the motor cortex evokes movement at each of the joints, and all possible movements about the joints can be elicited (Kwan *et al.*, 1978). The discharge of many of the cells in motor cortex can be related to the movements the animal makes, and cells can be found that fire in association with movements of the shoulder, elbow, wrist, hand or fingers (Lemon *et al.*, 1976). Many of these cells fire in relation to small precise movements (Fromm and Evarts, 1977). This electrophysiological evidence would suggest that the monkeys with sensorimotor lesions may be more disabled than they appear at first sight.

It was for this reason that we carried out a further investigation of the use of the forelimb in the 2 adult monkeys. The slot task appeared to make two demands on the animal, that it move its fingers independently and that it turn the wrist so as to allow the fingers to enter with the appropriate orientation. Tests were therefore devised so as to examine separately the use of the fingers and the wrist. Neither of the adult monkeys could push a single finger through a small hole while tucking the other fingers out of the way, even though in this task there was no requirement that the animal grasp the food. In the second task the monkeys had to knock food off a ledge by adducting or abducting the wrist. Neither monkey could abduct the wrist to any significant degree. The task proved less successful as a test for adduction of the wrist since these animals could cheat by flexing the wrist to reach many of the positions to their left. Nonetheless one animal failed to reach the two most extreme positions on that side.

It was noted that neither animal ever fed itself with the right hand, always transferring food from the right to the left hand when feeding. Monkeys normally bring food to the mouth by supinating the forearm so as to bring the fingers to the lips. The test for supination required the monkey to turn the forearm so as to reach food and knock it off the shelf. The results on this task are not easy to interpret, since one monkey (ASM14) would not attempt the task at all with the right hand, whereas the other monkey (ASM13) succeeded in supinating to a limited degree. If the food was located in the middle distance the monkey could raise its elbow and thus compensate for the limited degree to which it could supinate. If the food was presented close by it was not possible to raise the elbow, and if the food was presented at a distance the elbow had to be extended. It was at these positions that monkey ASM13 had trouble. However, since its reach was not as good with the right hand as with the left its lack of success with the far positions may partly reflect its poor reach.

The performance of the two adult monkeys on these tasks suggests that they had not recovered to the extent that might be supposed from casual observation. When they were tested in a setting in which their movements were restricted they turned out to have disabilities affecting not only the fingers but also the wrist and arm. These monkeys did not have a normal command of space. If their trunk was restricted they were no longer able to move the affected hand into all regions of the space immediately in front of them. By analogy with a visual field defect they may be said to have had a defect in their motor field. And this defect appears to have been permanent.

This description of the effects of sensorimotor lesions corresponds well to the picture one might expect on the basis of electrophysiological studies of cells in sensorimotor cortex. Georgopoulos *et al.* (1982) trained monkeys to move their arms from an initial central position to one of 8 target positions arranged around a working surface. They found that cells in both motor cortex (Georgopoulos *et al.*, 1982) and area 2 of somatosensory cortex (Kalaska *et al.*, 1981) respond more when the monkey moves its arm in certain directions than in others. Furthermore many of the cells in both areas discharge differently according to the position of the animal's arm in space (Caminiti *et al.*, 1981).

In this series of recording studies the task used mainly involved movements of the muscles of the shoulder (Massey *et al.*, 1981). Yet lesion studies on monkeys have tended to emphasize their inability to make independent movements of the fingers. There are two reasons that have led to this stress on the disabilities of the hand. The first is that it is easier to set up good tests of grasping than of the use of the arm in space. The second is that the corticospinal paths are better developed in primates which have dextrous hands than in other animals that have paws or hooves. One crude index is provided by the number of fibres in the pyramidal tract: controlling for differences in body size the chimpanzee has 1.8 times as many pyramidal fibres as would be expected for a carnivore of the same size and 3.6 times as many as an ungulate (data from Heffner and Masterson, 1975; calculations from Passingham, 1981). It is tempting to relate these striking anatomical differences to differences in dexterity, but horses or cats differ from primates quite as much as in the more restricted movements of the forelimb. A monkey has greater flexibility at every joint and thus a greater command of the space in front and above it, as in feeding. To put it another way, it has a more extensive motor field.

Mechanisms of Recovery

There are two ways in which recovery of function might occur. The first possibility is that other areas of the brain might be so constructed that they could take over and perform some of the functions of the damaged area without the need for any anatomical changes. The second is that there might be alterations in the anatomical pathways that allow restitution of function.

The results reported here indicate that no other cortical or subcortical area can direct fine movements of the fingers if motor cortex is removed, whether in infancy or adulthood. It had already been shown by Lawrence and Hopkins (1976) that no compensation occurred after a bilateral section of the pyramidal tract in infancy. The present experiment demonstrates that such recovery is not possible even if motor cortex is removed in infancy from one hemisphere alone, as in monkey M2.

There are three cortical areas that might potentially exert some control after the unilateral removal of motor cortex. These are the motor cortex of the other hemisphere and the somatosensory and premotor cortex of the same hemisphere. It has been shown by Brinkman and Kuypers (1973) that motor cortex has some control over the reaching movements of the ipsilateral arm, but they found no evidence that it could direct the fine finger movements of that hand. In the present study the motor cortex ipsilateral to the affected arm was unable to assume the direction of such movements even in the infants which had been left for two years or more to recover.

The somatosensory area SI contributes fibres to the pyramidal tract (Kuypers, 1960); and it has been claimed that electrical stimulation of SI elicits movements of the contralateral limb even after removal of motor cortex (Woolsey *et al.*, 1952). A small proportion of cells in SI fire before a monkey flexes or extends the wrist, though the majority fire after initiation of the movement (Evarts, 1972). However, a monkey can still perform discrete finger movements after removal of somatosensory cortex either bilaterally (Case 7 of Lawrence and Hopkins, 1976) or unilaterally (Case S12 of the present study). Furthermore the only monkey with a complete lesion of the motor cortex, M2, was as impaired in picking out food from a slot as any monkey with a lesion of area 4+SI.

The premotor cortex (area 6) also contributes fibres to the pyramidal tract (Kuypers, 1960). Moll and Kuypers (1975) have studied the effects of a lesion that includes both the premotor cortex and the anterior bank of the arcuate sulcus. They report that the monkeys are poor at guiding their fingers visually according to the orientation of the slot, but note that the monkeys can still remove the food with dexterity when they can feel the orientation of the slot. In the present study the lesions in sensorimotor cortex spared much of the premotor cortex. Yet the intact tissue of premotor cortex was not able to assume the control of fine finger movements.

This study thus confirms the suggestion made by Lawrence and Kuypers (1968) that the control of fine finger movements requires a direct anatomical path between cortex and the motoneurons. In the rhesus monkey direct connections of this sort only originate in the hand and foot area of motor cortex (Kuypers and Brinkman, 1970).

But could there be a reorganization of the anatomical paths if the lesion was inflicted in infancy? The accompanying paper by Sloper *et al.* (1983) finds no evidence for significant anatomical changes in the infant monkeys described in this paper. They have examined the subcortical connections of the hemisphere ipsilateral to the affected limb. They find the normal pattern of projections from the sensorimotor cortex to the spinal cord, pons, superior colliculus, subthalamic nucleus, ventrolateral and centremedian nuclei of the thalamus, and striatum. They also report that there is an anomalous projection to the magnocellular part of the contralateral red nucleus. But this projection is very small. This picture is quite unlike that seen in the rat, in which extensive sprouting occurs in several structures after removal of sensorimotor cortex in neonatal animals (Leong, 1976).

This study has failed to find evidence of behavioural or anatomical compensation in infant monkeys. But this is not to say that such compensation could not occur under any circumstances. The cortical damage was inflicted after birth at a time when the pyramidal decussation was already formed (Humphrey, 1960). In rats the decussation is not complete at birth and anatomical reorganization is still possible after a unilateral cortical lesion (Castro, 1975). Similarly, in hamsters the pyramidal fibres have not made all their terminations until some days after birth, and it is still possible for some fibres to establish connections if the tract is sectioned rostral to the decussation in neonatal animals (Kalil and Reh, 1982). Reh and Kalil (1982) report that if the pyramidal tract is cut on one side in adult hamsters they are poor at shelling sunflower seeds, but if the lesion is inflicted within a few days of birth the hamsters are able to develop the normal degree of skill at this task. However, this result needs checking, since the degree of extrapyramidal damage was much greater in the adults than the infants.

The crucial factor seems to be the degree of maturity of the brain at the time when it is damaged. A crude measure of maturity is given by the relative size of the infant brain compared with the adult brain. In the rat (*Rattus norvegicus*) the brain is only 11.8 per cent of its adult weight at birth, and in the golden hamster (*Mesocricetus auratus*) the figure is as low as 5.4 per cent; yet a neonatal rhesus monkey has a brain that is 48.1 per cent of its adult size (Sacher and Staffeldt, 1974).

If it is the maturity of the brain that matters it should be possible to demonstrate reorganization in the monkey brain if a lesion is inflicted early enough. Goldman and Galkin (1978) have removed the dorsal prefrontal cortex in one rhesus monkey 106 days after conception, at a time when the cells have not completed their migration to this area. This lesion resulted in the formation of a deep sulcus near the lateral border of the prefrontal cortex; a sulcus of this size and orientation is not seen if the prefrontal lesion is made 50 days or 18 months after birth. Furthermore, if the prefrontal cortex is damaged in infant or adult monkeys, retrograde degeneration takes place in the mediodorsal nucleus of the thalamus; but this did not occur in the monkey which was operated on before birth. Finally at the age of 2 years the monkey was able to succeed on delayed response tasks which are failed by monkeys in which the prefrontal lesion is inflicted in adulthood.

Such recovery does not occur if the dorsolateral prefrontal cortex is removed in monkeys after birth. When immature these monkeys do little worse on these tasks than normal infant monkeys of the same age (Harlow *et al.*, 1968; Tucker and Kling, 1967; Goldman, 1971); but they never develop the ability to perform on these tasks at an adult level (Goldman, 1974, 1976). It would, however, be worth investigating the effects of unilateral removals of prefrontal cortex in infant and adult monkeys. It has been shown that if dorsolateral prefrontal cortex is removed in the first 2 months after birth there is an increase in the number of fibres from the contralateral prefrontal cortex that terminate in the caudate nucleus ipsilateral to the damaged hemisphere (Goldman-Rakic, 1981). It is important to know whether this anatomical change is of any use to the animal.

These experiments indicate that the degree to which anatomical and behavioural reorganization is possible is determined by the maturity of the brain. A rhesus monkey with an age from conception of 106 days has a brain that is roughly 25 per cent of its adult size (calculated from data in Holt *et al.*, 1975). At this age the macaque brain is more comparable with that of the neonatal rat. If prefrontal cortex is removed in neonatal rats they are not impaired on delayed response tasks administered in adulthood (Kolb and Nonneman, 1978; Nonneman and Corwin, 1981). Furthermore, there is no retrograde degeneration in the mediodorsal nucleus of the thalamus in these rats (Kolb and Nonneman, 1978).

If it is assumed that anatomical reorganization is more likely to occur the less mature the nervous system, it is worthy of note that the human brain is less mature at birth than that of a monkey or ape. In a newborn baby the brain is only 25.8 per cent of its adult weight compared with 35.5 per cent for the chimpanzee (*Pan troglodytes*) and 50.0 per cent for the gorilla (*Gorilla gorilla*) (Sacher and Staffeldt, 1974). On this index the degree of maturity of the human brain at birth is roughly the same as that of the rhesus monkey on which Goldman and Galkin (1978) operated at the age of 106 days from conception. It is not until the baby is around 6 months old that its brain reaches the same level of maturity as the neonatal monkey or ape in terms of its weight relative to adult weight (Passingham, 1975).

If valid comparisons are to be made between species, data are needed on the level of maturity of the particular functional systems under consideration. For the human brain such data are scarce. But information is available on the size of the parvocellular laminae in the lateral geniculate body. In the rhesus monkey there is no significant growth in these after 8 days of age (Headon *et al.*, 1981) whereas they continue to grow in the human brain until 6 months of age (Hickey, 1977). It may be that there is greater scope for anatomical reorganization after early injury to the brain of a young baby than there is in the brain of an infant monkey.

CONCLUSIONS

There is an irony in the results of this study. It is not in dispute that there are circumstances in which animals may recover less well if lesions are inflicted in adulthood than in early life, whether before or after birth (Reh and Kalil, 1982; Goldman and Galkin, 1978; Kolb and Nonneman, 1978; Nonneman and Corwin, 1981). But it has not proved possible to demonstrate greater recovery in infant monkeys in which the sensorimotor cortex has been removed. Yet it was on the basis of her studies of recovery after motor lesions that Kennard (1942) based her influential claims. It is worth attempting to specify what conditions must be met if the 'Kennard Principle' is to hold. There are three issues.

1. There is no good evidence that the function of any area of neocortex can be 'taken over' by a different area of cortex. Kennard (1938) claimed that 'the highly developed and coordinated motor performance in the monkey deprived of motor and premotor tissue in infancy is due to integration from the other cortical regions, namely the frontal association areas and the postcentral regions'. But in the present study neither premotor cortex nor somatosensory cortex proved capable of directing the fine movements of the fingers and wrist, and there was no evidence that the infant monkeys were more coordinated in their general motor performance than the adults.

This is not to say that other brain areas do not contribute to the animal's recovery. They can do so without altering their normal functions. Thus it is known that in young monkeys the caudate nucleus plays an important role in enabling the monkey to solve delayed response tasks: infant monkeys are very impaired if the caudate is damaged (Goldman, 1974). As the monkeys grow up the maturing prefrontal cortex enables them to perform on this task with increasing proficiency. If the prefrontal cortex is damaged in an infant monkey the animals can still solve the task a year later. But this is not because the caudate nucleus has 'taken over' the function, but rather because it continues to function in its normal way.

2. The second issue is whether a cortical area in one hemisphere can perform the functions carried out by the same area in the other hemisphere if the latter is removed. The present experiment indicates that the motor cortex on one side is unable to direct the fine finger movements of the ipsilateral hand even if the motor cortex on the other side is removed in infancy. However, if an area of association cortex is removed in monkeys the homologous area in the other hemisphere can continue to direct the relevant function. After unilateral lesions of inferotemporal cortex (Ettlinger and Gautrin, 1971) or prefrontal cortex (Warren and Nonneman, 1976), monkeys are only slightly if at all impaired at performing the relevant tasks. Indeed, even after removal of one hemisphere, monkeys can still solve complex matching tasks to a normal level (Nakamura and Gazzaniga, 1978). The monkey brain is so organized that there is considerable redundancy between the functions of the association areas of the two hemispheres. Since this is true of adults as well as infants we should not expect to find greater recovery if damage is inflicted early in life.

In man, however, the organization of the neocortex is different. There is much less redundancy since each hemisphere is specialized for different functions (Levy, 1977). If a right-handed person suffers damage to the speech areas in the left hemisphere recovery is limited to the extent that the homologous regions of the right hemisphere are now committed to the direction of other functions. Recovery is more complete in those left-handers in whom there is evidence that both hemispheres played a role in language function before the injury; in such patients the intact areas continue to perform as before. In very young children either hemisphere can assume the direction of language and the removal of the dominant hemisphere neither prevents the acquisition of speech nor greatly interrupts it (Basser, 1962). Language can be recovered because in young children neither hemisphere is wholly responsible for it. The same point has been made by Cowey and Perry (1981).

3. The last question is under what conditions anatomical reorganization can promote functional recovery. There is no *a priori* reason why it should be supposed that alterations in anatomical connections must always compensate for the loss of cortical tissue. Schneider (1979) has reviewed the evidence that if one tectum is removed in neonatal hamsters, the fibres of the optic tract form anomalous terminals in the lateral posterior nucleus of the thalamus and in the remaining tectum. However, he stresses that the animals are hindered as much as helped by the unusual pattern of innervation.

Perry and Cowey (1982) concluded on the basis of similar studies in rats that some of the 'anomalous' projections are present at birth in the normal animal. A neonatal lesion not only preserves these anomalous projections but also results in a marked loss of ganglion cells from the retina. In spite of the preservation of these abnormal projections rats suffer a greater loss of acuity if the tectum is removed in infancy rather than in adulthood (Cowey *et al.*, 1982).

The most convincing demonstrations of true recovery are those in which the lesion was inflicted early enough to allow the re-establishment of a relatively normal anatomical pattern. Thus if the pyramidal tract is cut in a neonatal hamster, pyramidal fibres can still establish terminations in the contralateral spinal cord (Kalil and Reh, 1982). If cortical tissue is removed in a monkey before the cells have finished their migration, cells can still arrange themselves into a cortical structure, even if their exact destination is altered (Goldman and Galkin, 1978).

In the experiment of Lawrence and Hopkins (1976) the pyramidal tract was cut bilaterally after the formation of the pyramidal decussation. Even though the pyramidal cells had not made all their final terminations (Kuypers, 1962) it was not possible for the normal pattern of terminations to be re-established. In the present experiment the sensorimotor cortex was removed long after the cortical cells had finished their migration. In neither experiment did the infants appear to be less handicapped than the adults.

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AN ANATOMICAL STUDY OF THE EFFECTS OF UNILATERAL REMOVAL OF SENSORIMOTOR CORTEX IN INFANT MONKEYS ON THE SUBCORTICAL PROJECTIONS OF THE CONTRALATERAL SENSORIMOTOR CORTEX

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SUMMARY

Following removal of the motor or sensorimotor cortex in infant monkeys the projections of the remaining motor or sensorimotor cortex have been studied after long-term survival to look for anomalous projections from these areas. The patterns of degeneration resulting from lesions of the remaining motor or sensorimotor cortex corresponded to those found in normal adult monkeys in the spinal cord, pontine nuclei, superior colliculus, parvocellular red nucleus, subthalamic nucleus and thalamus. Sparse degeneration was found in the magnocellular part of the contralateral red nucleus which has not been described in normal animals and there is also the possibility of an increase in the crossed corticostriate projection. Infant monkeys do not form anomalous projections comparable to those found in the rat following neonatal sensorimotor cortex lesions.

INTRODUCTION

It has generally been held that recovery from the effects of neurological damage is more complete in infant than in adult animals (*see* Kennard, 1942). A possible reason for this could be the sprouting of new connections from remaining pathways to take over sites vacated by the pathways which degenerate as a result of the initial brain damage. Such sprouting has been described in rats following lesions which destroy one motor cortex in the first few days of life when pyramidal tract axons give rise to anomalous projections to the ipsilateral spinal cord, contralateral pons and contralateral superior colliculus (Hicks and D'Amato, 1970; Leong and Lund, 1973; Castro, 1975; Leong, 1976). Such new connections are not formed following similar lesions in adult rats. Because of the potential importance of such findings we have investigated this problem in the primate by studying the projections of the remaining motor or sensorimotor cortex in monkeys in which the motor or sensorimotor cortex of one hemisphere has been removed shortly after birth and a prolonged recovery period allowed.

If such sprouting occurred in the primate it would be important to establish whether it was of functional significance. The motor performance of these animals has therefore been extensively tested after a long recovery period and before removal of the second motor or sensorimotor cortex and compared with that of animals in which similar lesions have been made as adults and a similar long recovery period allowed. The behavioural findings are reported in the preceding paper (Passingham *et al.*, 1983).

MATERIAL AND METHODS

Under ether anaesthesia and using aseptic precautions the motor or sensorimotor cortex of 8 infant Rhesus monkeys was removed by suction at between seven days and three months of age and the infants returned to their mothers. After recovery periods of between two and a half and four years during which behavioural testing was carried out, 6 of the monkeys were again anaesthetized with pentobarbitone and the contralateral motor or sensorimotor cortex removed by suction. Five to ten days later the animals were again anaesthetized and perfused with normal saline followed by 10 per cent formalin. The remaining 2 animals were similarly perfused to test for residual degeneration from the initial operation; in one of these animals an eye was removed five days before perfusion to test for the adequacy of the staining of degeneration in this brain. After several weeks of fixation in 10 per cent formalin two blocks containing the region around the initial lesion were carefully dissected out, soaked in alcohol-acetic acid, embedded in paraffin wax, cut and stained by the Nissl method. Histological reconstructions of these lesions have been published with the behavioural studies (Passingham *et al.*, 1983). The remainder of the brain and blocks of cervical (C7–8), thoracic (approx. T6) and lumbar (L2–4) spinal cord were soaked in 30 per cent sucrose until they sank and frozen sections were cut. Series of sections were stained using the Fink-Heimer or Wiitanen modifications of the Nauta method. In addition a series of sections from each brain was mounted and stained using the Nissl method.

RESULTS

In 3 animals the left motor cortex alone was removed and in 5 both the left motor and somatic sensory cortices were removed at between seven days and three months of age (Table). After a long-term survival 2 animals with sensorimotor lesions were

TABLE DETAILS OF OPERATIONS

Animal	*Age at first operation (days)*	*Lesion (cortical area)*	*Age at second operation (months)*
M1	7	4	47
M2	72	4	36
M3	10	4	35
SM4	26	4+S1	36
SM5	89	4+S1	Control
SM6	23	4+S1	42
SM7	14	4+S1	32
33B	29	4+S1	Control

perfused to determine the extent of any residual degeneration and in the remaining 6 animals the distribution of degeneration was studied shortly after a lesion of the intact motor or sensorimotor cortex of the opposite hemisphere. Since the normal projections of the primate sensorimotor cortex have been described in detail by a number of authors using both degeneration and autoradiographic methods such details will not be repeated here. Attention will be concentrated on any differences from these descriptions and particularly on sites where the normal projection is unilateral or where sprouting has been described in the rat.

As it was necessary to study the subcortical projections of the whole motor or sensorimotor cortex in these animals, axonal degeneration methods have been used in preference to autoradiographic tracing techniques. Whereas it was possible to be reasonably confident about the complete removal of the motor or sensorimotor cortex it would have been difficult to inject radioactive amino acids uniformly throughout such a large area of cortex; a large part of this cortex is buried in the central sulcus and the depth of the sulcus varies considerably along its mediolateral extent. Complete removal of these cortical areas was of particular importance in allowing comparison of the projections of the cortex containing the representations of different parts of the body.

Residual Degeneration

Coarse residual degeneration was still present in the internal capsule, medullary pyramid and corticospinal tracts but residual terminal degeneration was not present in any of the projection sites studied although occasional isolated coarse fibres could be seen in some sites. Well-stained degeneration was present in the lateral geniculate nucleus of one control animal in which an eye was removed five days before perfusion.

Experimental Animals

Spinal cord. Sections were studied at cervical (C7–8), midthoracic (approximately T6) and lumbar (L2–4) levels from each animal. Extensive degeneration was present bilaterally at all three levels (fig. 1) with a distribution which corresponded closely to that described by Kuypers (1960), Liu and Chambers (1964) and Kuypers and Brinkman (1970). In particular, only very occasional degenerating fragments were present among the motor neurons in the lateral part of the ventral horn on the side ipsilateral to the second lesion, although degeneration was present in the lateral motor neuron pool of the opposite side.

Pontine nuclei. Heavy degeneration was present in the pontine nuclei ipsilateral to the second lesion and corresponded in distribution to that described by Brodal (1978) following motor or sensorimotor cortex lesions. A little sparse degeneration was also present in the contralateral pontine nuclei, usually symmetrical to the ipsilateral foci (fig. 1). This contralateral degeneration was similar in amount to that seen after sensorimotor lesions in normal monkeys (Brodal, 1978) or using autoradiography (Hartmann-von Monakow *et al.*, 1981). No evidence was found of

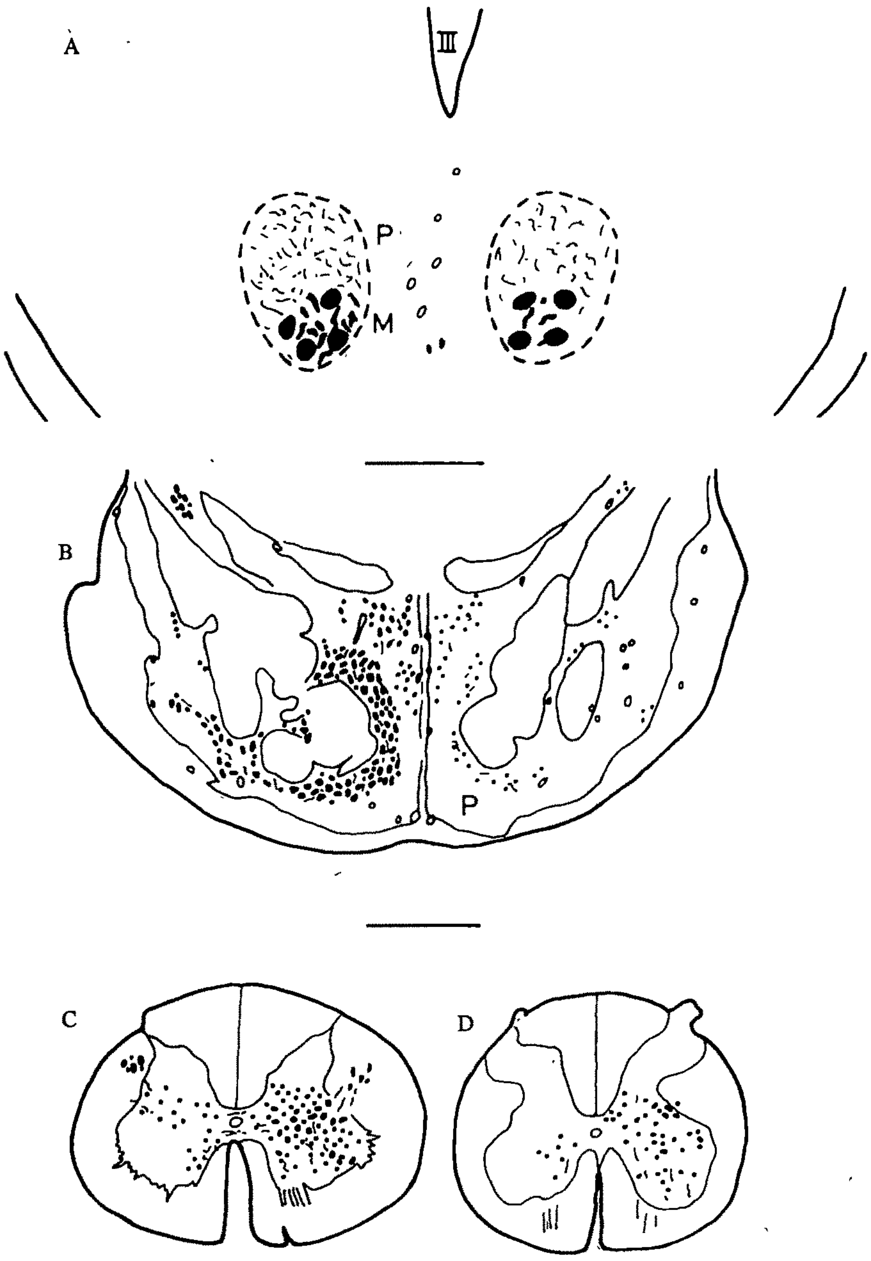

FIG 1. Diagram showing the distribution of degeneration in the red nucleus, pontine nuclei and spinal cord of a monkey seven days after removal of the right motor cortex, the left motor cortex having been removed postnatally. A, distribution of degeneration in the parvocellular (P) and magnocellular (M) parts of the red nucleus ipsilateral (*left*) and contralateral (*right*) to the second motor cortex lesion. B, distribution of degeneration in the pontine nuclei (P) ipsilateral (*left*) and contralateral (*right*) to the second motor cortex lesion. C, D, distribution of degeneration in the cervical (C) and lumbar (D) spinal cord contralateral (*right*) and ipsilateral (*left*) to the second motor cortex lesion.

degenerating axons sprouting across the midline as has been described in the rat (Leong, 1976).

Superior colliculus. A little degeneration was present in the laterobasal part of the superior colliculus ipsilateral to the second lesion as in the normal monkey (Kuypers and Lawrence, 1967; Hartmann-von Monakow *et al.*, 1979), but no evidence of sprouting to the contralateral superior colliculus was seen.

Red nucleus. Heavy degeneration was present bilaterally in the parvocellular red nucleus, with more degeneration on the side ipsilateral to the second lesion (fig. 1). This distribution corresponds to that described in normal monkeys (Kuypers and Lawrence, 1967; Hartmann-von Monakow *et al.*, 1979). Rather coarser and considerably less dense fibre degeneration was present in the magnocellular part of the red nucleus ipsilateral to the second lesion. In addition, sparse but definite coarse fibre degeneration was present in the magnocellular part of the red nucleus contralateral to the second lesion in animals with motor and sensorimotor cortex lesions (figs. 1 and 2). Fibres entered from the dorsal aspect of the nucleus as on the ipsilateral side. There were no obvious differences in this degeneration between animals whose initial operation was early (1 week) or later (up to 3 months of age). No residual degeneration was present in the red nucleus of the control animals. In normal animals the projection from the motor cortex to the contralateral red nucleus is restricted to the parvocellular part using both degeneration methods (Kuypers and Lawrence, 1967) and autoradiography (Hartmann-von Monakow *et al.*, 1979).

Subthalamic nucleus. Degeneration was present only in the subthalamic nucleus ipsilateral to the second lesion, confirming previous descriptions of this projection in normal monkeys (Petras, 1969; Hartmann-von Monakow *et al.*, 1978).

Thalamus. Degeneration in the ventrolateral nucleus was present only ipsilateral to the second lesion whereas degeneration was present bilaterally in the centre-median nucleus, with considerably more on the ipsilateral side. For both nuclei this confirms the projections described in normal monkeys (Kuypers, 1966; Kunzle, 1976). Extensive retrograde changes were present in the Nissl stained sections of the ventrolateral nucleus on the side of the original lesion in animals with motor cortex lesions and in the ventrolateral and ventral posterior nuclei of animals with sensorimotor lesions.

Striatum. On the side ipsilateral to the second lesion degeneration was present in the dorsolateral part of the putamen distributed as described following motor or sensorimotor cortex lesions in normal monkeys (Kemp and Powell, 1970; Kunzle, 1975; Jones *et al.*, 1977). Degeneration was also present in the corresponding region of the contralateral putamen. This was considerably less dense and less widely distributed than the ipsilateral degeneration. A projection from the motor cortex to the contralateral striatum has not been described in normal adult monkeys using degeneration methods (Kemp and Powell, 1970), but a comparable contralateral projection has been described using autoradiography (Kunzle, 1975; Jones *et al.*, 1977).

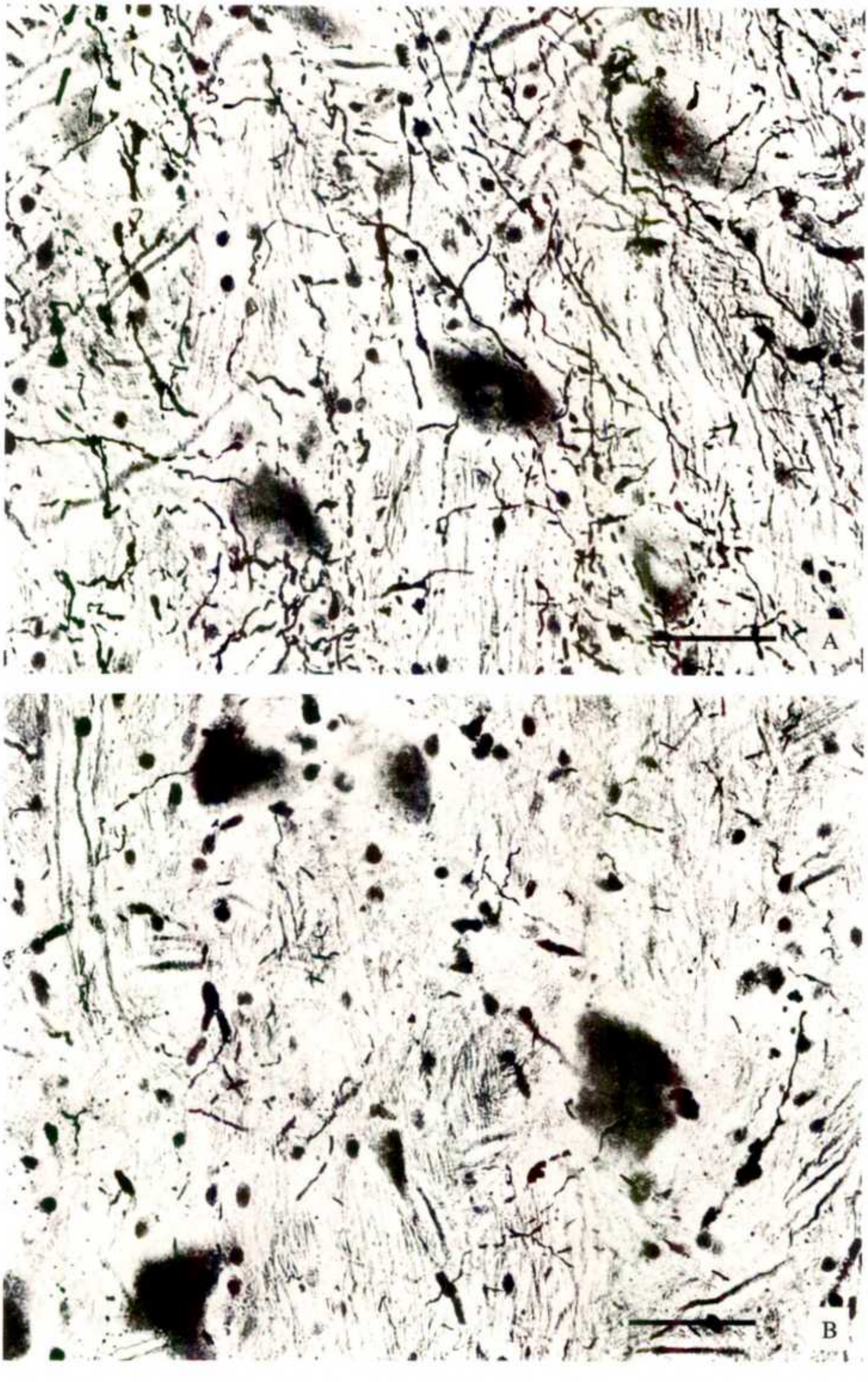

FIG. 2. Fibre degeneration in the magnocellular part of the red nucleus of a monkey (M1) seven days after removal of the right motor cortex, the left motor cortex having been removed at one week of age. A, coarse degeneration ipsilateral to the second motor cortex lesion. B, sparse degeneration contralateral to the second motor cortex lesion. No crossed projection to the magnocellular part of the red nucleus has been described in normal adult monkeys. (Bars = 100 μm.)

DISCUSSION

This study has examined the projections of the remaining motor or sensorimotor cortex following neonatal removal of the corresponding cortical area of the other hemisphere. In the rat, neonatal lesions involving the motor cortex produce anomalous projections to the ipsilateral spinal cord, contralateral pons and contralateral superior colliculus (Hicks and D'Amato, 1970; Leong and Lund, 1973; Castro, 1975; Leong, 1976). In the monkey, following neonatal lesions, the distribution of fibres from the remaining motor cortex to these three sites corresponds closely to that seen in normal animals and there is no evidence of anomalous projections. Similarly, the projections from the motor cortex to the subthalamic nucleus and ventrolateral nucleus of the thalamus which are normally strictly unilateral show no evidence of bilaterality in these experimental monkeys. In the remaining three sites examined, the striatum, red nucleus and the centremedian nucleus of the thalamus there is normally a substantial crossed projection in addition to the ipsilateral connection which makes it more difficult to determine the presence or absence of any changes in the crossed fibres. In the centremedian nucleus and the parvocellular part of the red nucleus, the contralateral projections were very similar in these experimental animals to those in normal animals and it is unlikely that substantial change had occurred. In the striatum and magnocellular red nucleus there were differences from normal animals.

In the magnocellular red nucleus contralateral to the second motor or sensorimotor lesion a few coarse degenerating fibres were consistently present. The motor cortex projection to the magnocellular part of the red nucleus has been described as being restricted to the ipsilateral side in normal animals both using degeneration methods (Kuypers and Lawrence, 1967) and the more sensitive autoradiographic technique (Hartmann-von Monakow *et al.*, 1979) and no residual degeneration was present in this site in the control animals used in this study. It seems likely, therefore, that these fibres represent a sparse anomalous projection extending in from the adjacent parvocellular part of the nucleus. This is similar to the anomalous translaminar sprouts seen in the lateral geniculate nucleus of the cat following neonatal removal of an eye. These are similarly very sparse and are an extension from an adjacent normal projection. Whether the small number of degenerating fibres found in the contralateral magnocellular red nucleus is of much functional significance remains to be determined. It is of interest, however, that there is both anatomical and physiological evidence of plasticity of the corticorubral projection in adult cats (Nakamura *et al.*, 1974; Tsukahara *et al.*, 1975).

Following the second motor or sensorimotor cortex lesions, a considerable amount of degeneration was present in the contralateral striatum of these monkeys. No degeneration was found in the contralateral striatum following lesions restricted to the motor or somatic sensory cortex in a previous study using degeneration techniques (Kemp and Powell, 1970), but a substantial crossed corticostriate projection arising in the motor cortex has been described using autoradiographic methods (Kunzle, 1975; Jones *et al.*, 1977). It is therefore difficult to assess the significance of this finding, but in view of the plasticity demonstrated in the primate corticostriate projection following prenatal lesions of frontal association cortex (Goldman, 1978), there is also the possibility of some sprouting in the present experiments.

Following neonatal removal of motor or sensorimotor cortex we have thus found little evidence of any significant change in the subcortical projections of the remaining sensorimotor cortex to replace the connections from the contralateral side. However, it is worth noting that there is already considerable bilaterality in the projections of the normal motor cortex to the striatum, the centremedian nucleus of the thalamus, the parvocellular part of the red nucleus and the medial and dorsal parts of the spinal cord. Although new connections are not formed, the remaining motor cortex has considerable potential access to motor neurons controlling trunk and limb muscles, either directly in the spinal cord or through that part of the rubrospinal tract arising in the parvocellular red nucleus (Kneisley *et al.*, 1978) and may contribute substantially both to the normal function and to the recovery of the ipsilateral limbs. Indeed it may be that, as with frontal lesions, the contralateral side is substantially masking the deficit produced by motor cortex removal. There is, however, no ipsilateral projection to the lateral motor neuron groups and this is in accord with the lack of recovery of independent finger movements seen in these animals (Passingham *et al.*, 1983).

Passingham *et al.* (1983) have considered in some detail possible mechanisms of recovery in these monkeys in relation to their behavioural results and have discussed reasons for the lack of sprouting in monkeys compared with rats. It seems likely that the virtual absence of plastic change in monkeys operated postnatally is related to the relative maturity of the monkey brain at birth compared with that of the rat. Recent evidence in the cat suggests that it may be more specifically related to the maturity of particular fibre systems at the time of surgery (Bregman and Goldberger, 1982). Although it has usually been assumed that anomalous projections are the result of sprouting from existing axons, it is now clear in a number of instances in the mammal that transient widespread axonal connections are formed during development and these subsequently retract to give the adult form of connectivity (Rakic, 1976; Innocenti *et al.*, 1977; Ivy *et al.*, 1979; Land and Lund, 1979; LeVay *et al.*, 1980; O'Leary *et al.*, 1981; Stanfield *et al.*, 1982). At least some anomalous projections result from the persistence of such transient connections formed normally during development and whether these persist or not depends on whether the lesion is made before or after they retract naturally. Interpretation of the results of such experiments therefore requires knowledge of the normal pattern of connections at the time the lesion is made as well as at the time of the final experiment.

ACKNOWLEDGEMENTS

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BENIGN X-LINKED MYOPATHY WITH ACANTHOCYTES (McLEOD SYNDROME)

ITS RELATIONSHIP TO X-LINKED MUSCULAR DYSTROPHY

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SUMMARY

Two healthy men with McLeod syndrome, a rare X-linked recessive phenotype characterized by acanthocytosis and weakened red blood cell antigenicity in the Kell blood group system, have been investigated. Both men showed raised blood creatine kinase levels, with myopathic EMG abnormalities. Biopsies of the quadriceps muscle showed the features of an active myopathy although there was no clinical evidence of muscular abnormality. The combination of the association of membrane abnormalities in red blood cells and a myopathy in both McLeod phenotype and Duchenne muscular dystrophy suggests that these syndromes may be due to related genetic abnormalities. The genetic locus for McLeod phenotype is situated near the end of the short arm of the X chromosome. The locus for Duchenne muscular dystrophy is unknown but it has been postulated that it is also situated on the short arm of the X chromosome at Xp 21. The occurrence of a subclinical X-linked myopathy with acanthocytosis (McLeod phenotype) thus raises the possibility of a new approach to genetic investigations in Duchenne muscular dystrophy, and in the related milder forms of this disease.

INTRODUCTION

Several varieties of X-linked myopathy have been described. The commonest of these is Duchenne muscular dystrophy (Duchenne, 1868) and this is the most severe, beginning in infancy and causing severe disability before the age of 10 years. In 1955 Becker and Kiener described a less severe form of X-linked muscular dystrophy. This disease begins after the age of 8 years and severe disability develops about fifteen years later (Emery and Skinner, 1976). Other slowly progressive X-linked myopathies have been reported in which the age of onset of weakness was later, and the rate of progression was slower than in patients with Becker muscular dystrophy (Mabry *et al.*, 1965; Ringel *et al.*, 1977). Emery and Dreifuss (1966) described a clinically distinct X-linked muscular dystrophy in which flexion contractures of elbows and tendo Achillis were prominent, but in which pseudohypertrophy was not a feature. In addition, X-linked forms of scapuloperoneal myopathy (Thomas *et al.*, 1972) and myotubular myopathy (van Wijngaarden *et al.*, 1969) have been described.

The McLeod phenotype (Allen *et al.*, 1961) is a rare X-linked condition in which the red blood cells show acanthocytosis, anisocytosis and dacrocytosis (Wimer *et al.*, 1977) and reduced *in vivo* survival (Marsh, 1978*a*). In the McLeod syndrome, inheritance of a variant allele, X^2k or X^4k prevents synthesis of the Kx antigen. It has been suggested that the Kx antigen is a marker for a precursor substance necessary for production of Kell antigens on red blood cells, and in McLeod phenotype there is reduced Kell antigenicity on red blood cells (Marsh, 1978*a*). Absence of Kx antigen from leucocytes, which may or may not be associated with absent Kx antigen on red blood cells, that is, with McLeod phenotype itself, is associated with X-linked chronic granulomatous disease. In the latter syndrome there is increased susceptibility to bacterial infection because affected leucocytes have reduced bactericidal activity against infected micro-organisms (Marsh *et al.*, 1975*a*; Segal and Peters, 1976; Densen *et al.*, 1981). Although no clinical evidence of muscular disease has been reported in McLeod phenotype, it has recently been noted that the blood creatine kinase level is raised in this condition and that this is the muscle isoenzyme (CKmm) (Marsh *et al.*, 1981). Although several different

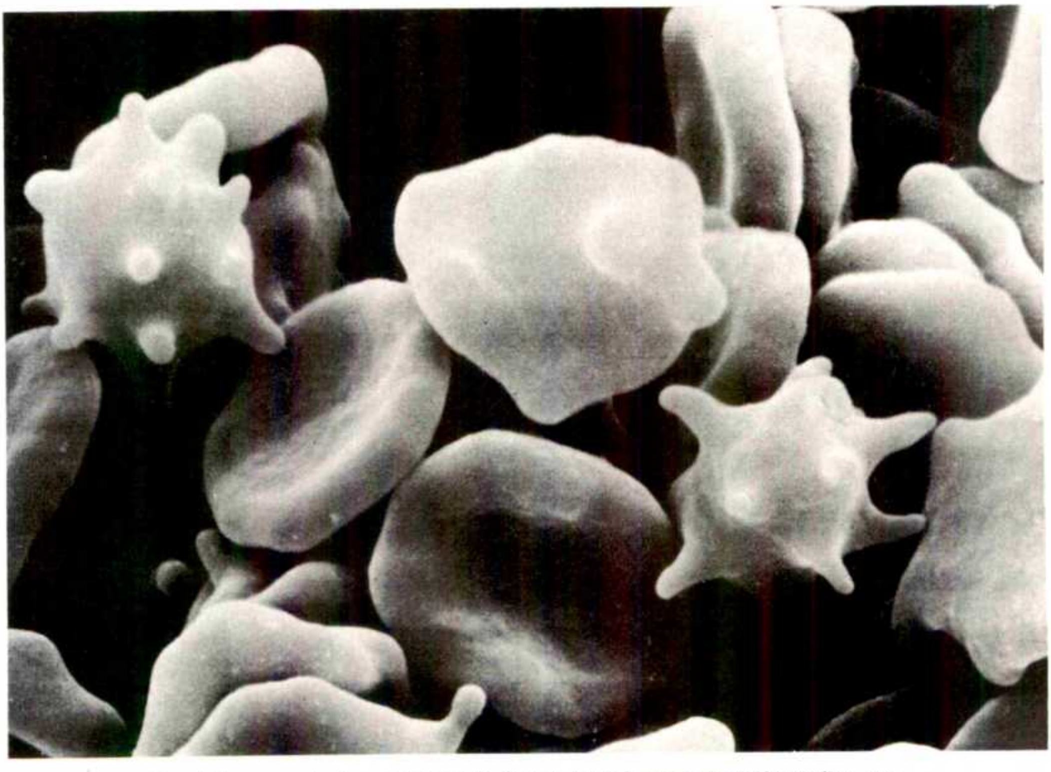

FIG. 1. Scanning electron micrograph, *Case 1*. Acanthocytic change in erythrocytes.

neurological syndromes have been associated with acanthocytosis in earlier reports (Estes *et al.*, 1967; Aminoff, 1972), in some of which neuromuscular involvement occurred, no neurological abnormality has hitherto been observed in people with McLeod phenotype.

We have investigated the neuromuscular system in two healthy men with the McLeod phenotype.

SUBJECTS

Two healthy men, aged 37 and 48 years, respectively, were studied. Neither had previously suffered from any neurological disorder, and there was no history of muscular weakness, fatiguability or cramps. Both were proficient sportsmen. There was no family history of neuromuscular disorder or other disease.

These two men came to our notice through the South London Transfusion Centre because they had been found to have McLeod phenotype and acanthocytosis (fig. 1) during screening as blood donors. This blood transfusion centre collects blood from about 100,000 different donors annually. In the three-year period 1976–1979, all donors' blood was tested with anti-k serum in a search for KK donors, of which approximately 300 were detected. Two of these donors were shown to be of the McLeod phenotype (Dr C M. Giles, Blood Group Reference Laboratory, and Dr P. Tippett, MRC Blood Group Unit). Studies of these two blood donors' families in the two laboratories revealed no other instance of McLeod phenotype (fig. 2).

RESULTS

Blood Group Serology

Both propositi gave reactions characteristic of the McLeod phenotype: K-kw, Kp(a-bw c –), Js(a-bw), Ul(a –), Wk(a –)K: –11, Ku w, KL –, Kx –. The families

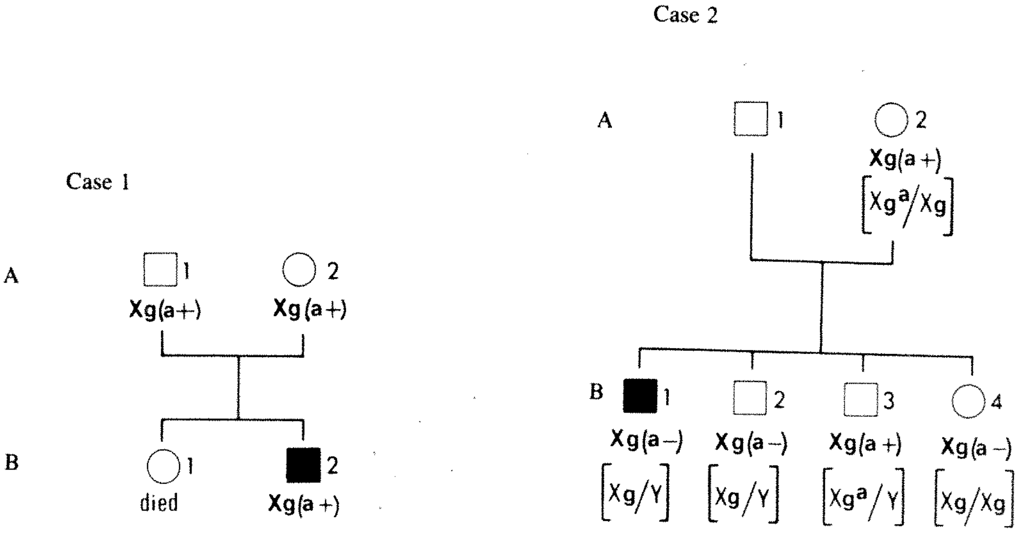

FIG. 2. Pedigrees of the two propositi showing the patterns of inheritance of the McLeod syndrome (marked in black) and of the Xg groups. These data were kindly supplied by Dr C. M. Giles and Dr P. Tippett.

of both propositi were tested. The mother of one showed two populations of red cells when tested with anti-k, $-\mathrm{Kp}^b$ and $-$Ku; the mother of the other did not. Neither of the mothers' blood contained acanthocytes.

Both families were tested with anti-Xg^a; the family of Case 2 was informative: mother Xg(a+), propositus Xg(a−), one normal brother Xg(a−) and the other normal brother Xg(a+) (fig. 2). Therefore there has been at least one recombinant between *Xg* and *Xk* in this family, provided that the McLeod phenotype of this propositus is not due to a mutation or to a background unrelated to *Xk*.

Clinical Examination

There was no neurological or neuromuscular abnormality. Both men were well-muscled, but there was no hypertrophy, weakness or change in muscle consistency to palpation. There was no myotonia, and the tendon reflexes were brisk and symmetrical. Venous blood was taken for creatine kinase and carbonic anhydrase III, a muscle-specific enzyme (Heath *et al.*, 1982). Liver function tests, routine haematological investigations and red blood cell morphology tests, including light and scanning EM studies, were carried out. An ischaemic lactate test was undertaken in both patients. Concentric needle and single fibre EMG studies, and motor and sensory nerve conduction measurements were performed. These included sampling of deltoid, biceps, quadriceps and extensor digitorum communis muscles, and nerve conduction studies in arms and legs. A needle biopsy was taken from the right quadriceps muscle, and routine enzyme histochemical and ultrastructural studies were made using frozen and resin-embedded material (Swash and Schwartz, 1981).

Biochemistry

The resting creatine kinase levels were raised in both patients (Table 1); it was about eight times normal in Case 1, and about four times normal in Case 2. The carbonic anhydrase III level was also raised to a greater extent in Case 1 than in Case 2. The hydroxybutyrate dehydrogenase was also raised to a greater degree in Case 1 than in Case 2, but the alanine transferase level was increased only in Case 1 (Table 1). The ischaemic lactate test showed a normal rise in venous blood

TABLE 1. BLOOD ENZYMES

	Case 1	*Case 2*
Resting creatine kinase (normal < 250 IU/l)	2068	1051
Carbonic anhydrase III (normal < 80 ng/ml)	335	130
Hydroxybutyrate dehydrogenase (normal 70–130 U/l)	287	157
Alanine transferase (< 35 U/l)	51	9

lactate following the period of ischaemic exercise, but the creatine kinase levels did not rise (Table 2). The carbonic anhydrase III levels rose in Case 1, but showed virtually no change in Case 2. In the control subject there was no marked change in enzyme levels during the test.

TABLE 2. ISCHAEMIC LACTATE TESTS (WITH ENZYME LEVELS)

	Case 1			*Case 2*			*Control*		
	Lactate (mg/l)	*CK (IU/l)*	*CA III (ng/ml)*	*Lactate (mg/l)*	*CK (IU/l)*	*CA III (ng/ml)*	*Lactate (mg/l)*	*CK (IU/l)*	*CA III (ng/ml)*
Resting	0.6	2068	335	0.6	1051	130	0.7	126	16
3 min	4.6	2101	400	1.1	952	135	1.3	129	20
8 min	4.2	2046	444	3.0	968	160	1.7	125	28
23 min	0.7	2079	345	0.9	930	135	0.9	120	22

CK = creatine kinase. CA III = carbonic anhydrase III.

Electromyography

In both patients motor conduction velocity in the median, ulnar and tibial nerves was normal, and sensory conduction was normal in the sural and median nerves. Concentric needle EMG studies revealed normal insertion activity in both patients. There were no fibrillation potentials or myotonia. On volition a number of polyphasic motor unit action potentials of normal or reduced amplitude were recorded in all the muscles studied in both patients. When the trigger-delay line was employed some of these polyphasic motor unit action potentials were of increased duration (greater than 10 ms). A full interference pattern was recorded with only moderate effort. These findings suggested a mild myopathic disorder. A single fibre EMG was carried out in the right biceps and extensor digitorum communis muscles (fig. 3). The motor unit fibre density was 2.2 in Case 1 and 2.3 in Case 2 (normal < 1.8, Stålberg and Thiele, 1975), and the neuromuscular jitter was increased in 15 per cent of potential pairs examined in both patients (normal < 5 per cent). No impulse blockings were recorded.

Muscle Histology

The muscle biopsy was abnormal in both cases (Table 3). Type 1 fibre predominance was found in both biopsies and type 2B fibres were absent in both cases. Fibre type differentiation was otherwise normal. There was no fibre type grouping in either case. Mild type 2 fibre atrophy was present in Case 2. There was a slightly increased variability in the diameter of the muscle fibres in Case 2, but the atrophy and hypertrophy indices were within normal limits (Dubowitz and Brooke, 1973). Central nucleation was increased in Case 2 (fig. 4), and in this biopsy a few fibres showed fibre splitting. Several clusters of small or necrotic and regenerating fibres were found in both cases (fig. 5). In Case 2 several fibres had a basophilic rim, which reacted positively for RNA in methyl green pyronine preparations and also for acid phosphatase activity. In these abnormal regions calcium was detected with

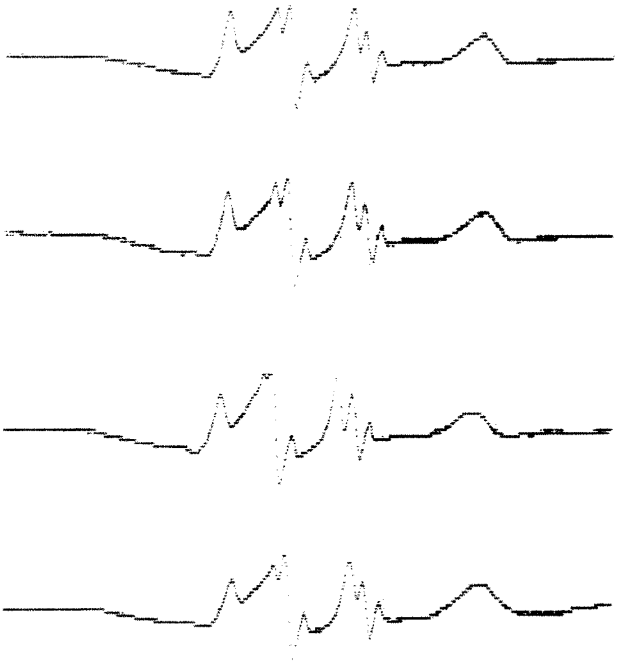

FIG. 3. Single fibre EMG, *Case 2.* (Sweep duration 10 ms.) Complex motor unit action potential. The neuromuscular jitter is normal.

the alizarin red technique (fig. 4). The necrotic fibres showed multiple small zones of positive staining with alizarin red. There were no inflammatory cell infiltrates and endomysial and interstitial fibrous tissue was normal. There were no rounded or hyalinized fibres.

Electron microscopy revealed that most muscle fibres were normal. The clusters of degenerating and regenerating fibres, consisting of three or four small adjacent fibres (fig. 5), seen in Case 2, showed abnormalities of their myofibrillar pattern, with

TABLE 3. MUSCLE BIOPSY FEATURES

	Case 1	*Case 2*
Type 1 fibres (%) (normal < 55%)	64	58
Type 2B fibres	Absent	Absent
Mean type 1 fibre diameter	60 ± 7.9 μm	64 ± 14.8 μm
Mean type 2 fibre diameter	61 ± 12.2 μm	59 ± 16.0 μm
Fibres < 30 μm	1%	3%
Central nucleation (normal < 4%)	1%	10%
Fibre splitting	Absent	A few fibres
Necrotic fibres	Present	Rare

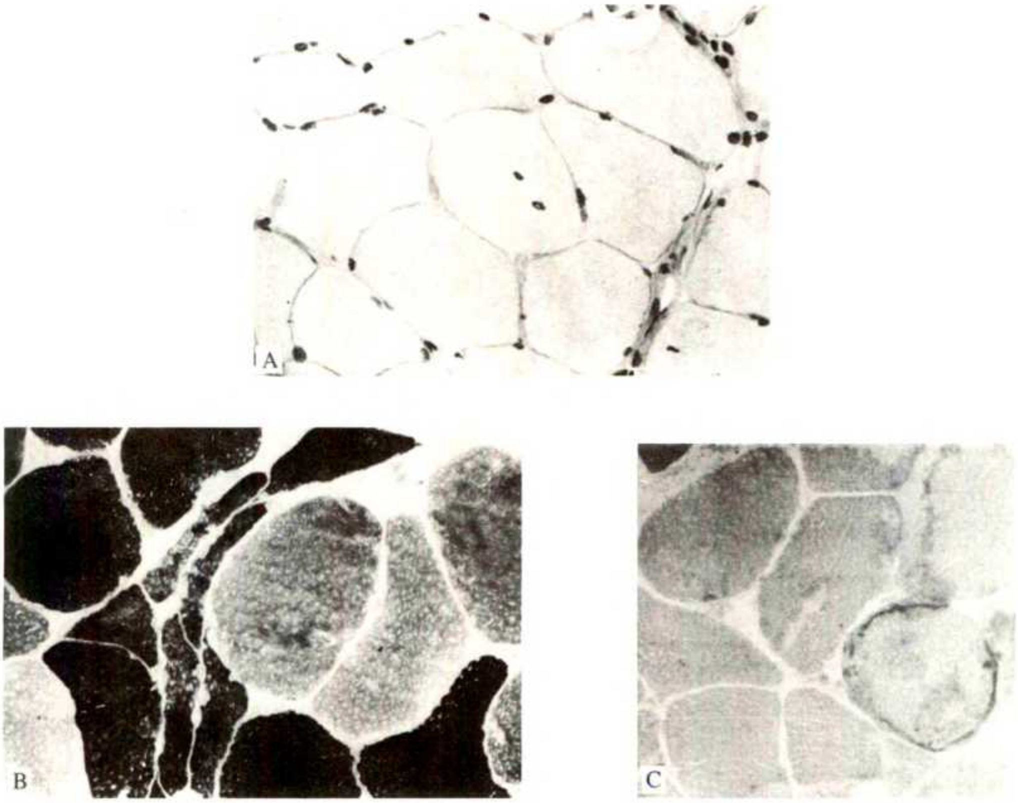

FIG. 4. A, one fibre contains two central nuclei. PAS ×400. B, a small cluster of atrophic fibres, probably representing regenerating fibres. ATPase pH 4.6 × 400. C, the rounded fibre shows a thin rim of positive reaction indicating calcium deposition. Alizarin red ×400.

increased amounts of glycogen. Their nuclei were slightly enlarged and showed a dispersed chromatin pattern. Their plasma membranes were intact, but showed a wavy outline in transverse section, although without reduplication of the basal lamina (fig. 6). Satellite cells were recognized in these fibres. Interstitial macrophages were present in association with these abnormal fibres, and in one a macrophage containing prominent lysosomal vacuoles was identified within its sarcoplasm. Golgi apparatus, tubules of the sarcoplasmic reticulum and mitochondria were prominent in the granular cytoplasm of these fibres, and the myofibrils consisted of scattered aggregations of thin filaments, some associated with dense Z band material. In these fibres ribosomes and polyribosomes were prominent suggesting that these myofibrillar changes were regenerative in type. Small blood vessels were normal.

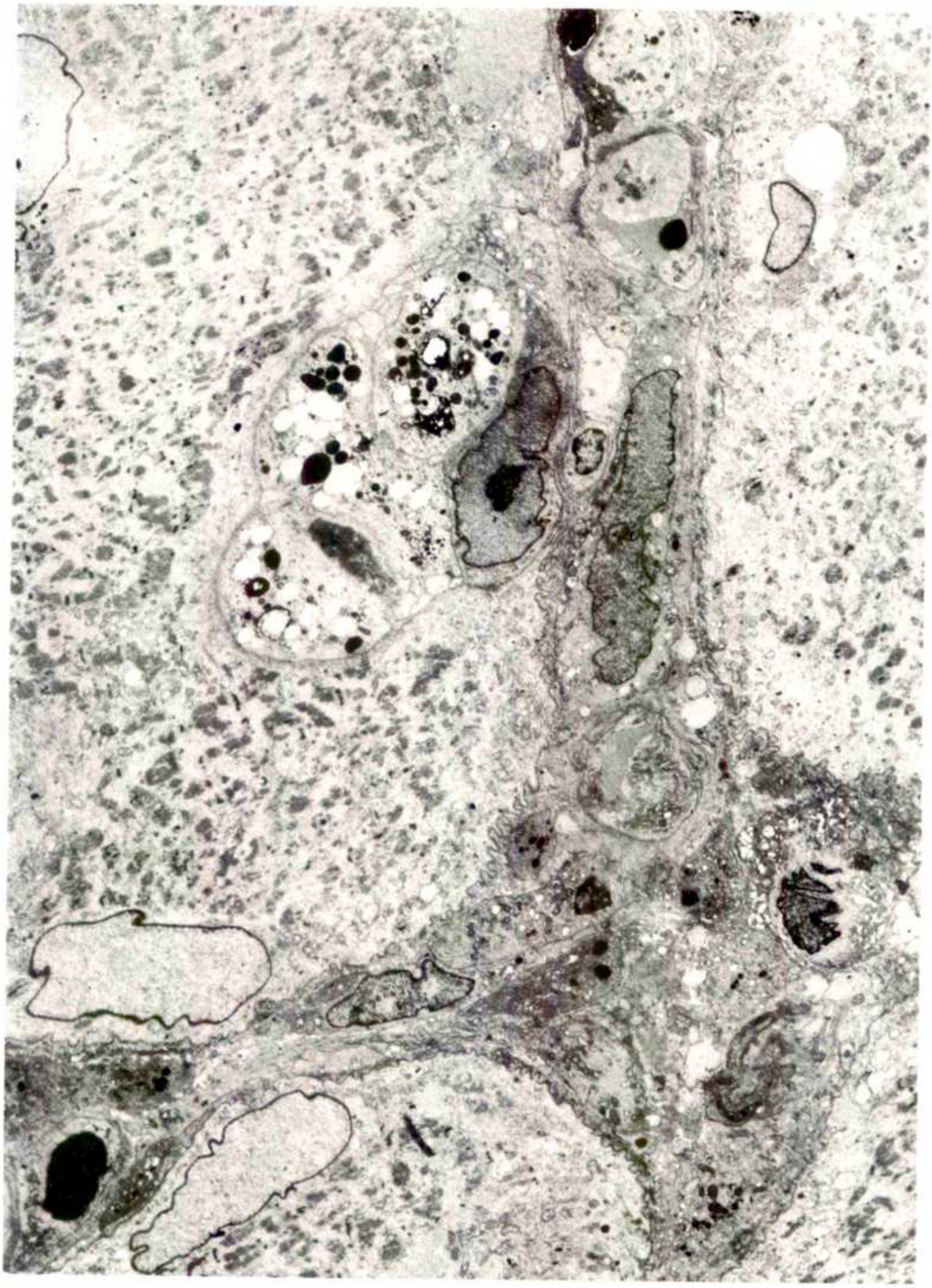

FIG. 5. A group of four adjacent muscle fibres undergoing regeneration. Their nuclei show a dispersed chromatin pattern and the myofibrils are widely separated and vary in size. One fibre contains a macrophage, itself containing vacuoles of autophagic type. Several capillaries lie between the four muscle fibres. EM × 2900.

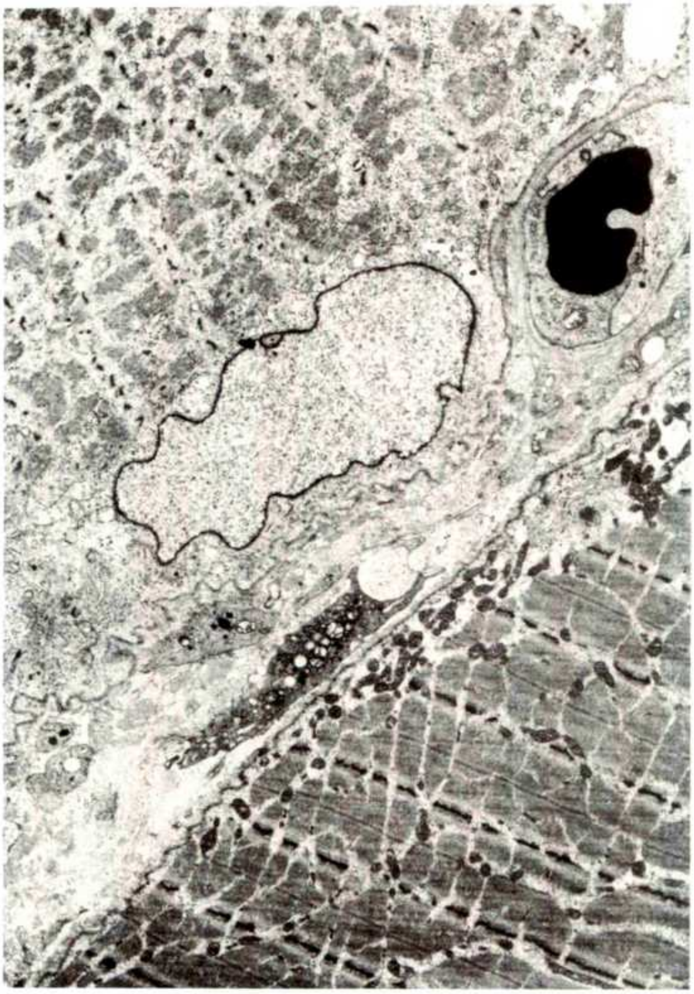

FIG. 6. A regenerating fibre situated adjacent to a normal fibre. Its plasma and basement membranes are convoluted but intact. EM ×4500.

DISCUSSION

Although these two men were asymptomatic and there was no clinically detectable neuromuscular abnormality, the raised blood creatine kinase levels, the abnormal conventional and single fibre EMG studies, and the abnormalities found in the muscle biopsies, all indicated the presence of an active myopathy. This myopathy showed no specific clinical or pathological features; indeed it was not clinically detectable. However, the association with McLeod phenotype in which the blood level of the muscle-derived isoenzyme of creatine kinase is invariably raised (Marsh *et al.*, 1981) suggests that this myopathy represents an abnormality in muscle fibres which forms part of this X-linked disorder. Although the myopathy in these two men was subclinical, the muscle biopsy showed features of active muscle fibre necrosis and regeneration, and it is possible that this might lead to clinically apparent weakness later in the course of the disease. In our patients there were slightly raised levels of circulating hepatic enzymes, an observation also made by Marsh *et al.* (1981), and this may indicate an associated abnormality in the liver.

The McLeod phenotype is inherited as an X-linked trait (Marsh, 1978*a*, *b*; Marsh *et al.*, 1981). The mothers of affected males, and other female carriers of the variant Xk allele, show red cell mosaicism, with both normal red cells of common Kell type and acanthocytes of the McLeod phenotype which lack the Kx antigen (Wimer *et al.*, 1977; Marsh *et al.*, 1981), a phenomenon consistent with the Lyon effect (Marsh *et al.*, 1981). In these female carriers the blood creatine kinase level is normal (Marsh *et al.*, 1981). Muscle biopsies of these carriers have not been studied.

TABLE 4. PHENOTYPES OF Xk VARIANT ALLELES*

Xk	*Kx antigenicity*			
Allele	*Leucocytes*	*Red cells*	*CK*	*Clinical features*
X^1k†	+ +	+	Normal	Normal people with common Kell blood group type
X^2k	—	—	Normal or slightly raised	McLeod phenotype and chronic granulomatous disease
X^3k	—	+	Normal	Normal red cells of common Kell type; chronic granulomatous disease
X^4k	+ +	—	Increased	McLeod phenotype

* Modified from Marsh *et al.* (1975*b*); Marsh (1978*a*). + Weakly positive. + + Strongly positive.
† An additional rare variant at the Kell locus exists which produces no Kell antigen, but allows an excess of unconverted Kx antigen on the red cells (*see* Marsh 1978*a*, *b*).

The Kx antigen is also associated with leucocytes, and four possible permutations of red blood cell and leucocyte phenotypes may arise through variants of alleles at the Xk locus (Table 4). Of these four phenotypes, two show the McLeod red cell phenotype. Patients with both chronic granulomatous disease and McLeod phenotype have normal or only slightly raised blood creatine kinase levels. The muscle of these latter patients has not been studied. Chronic granulomatous disease is due to an abnormality of leucocyte function, associated with reduced Kx antigenicity on leucocytes, in which there is an increased susceptibility to low-grade infections. This results from an abnormality in oxidative metabolism of monocytes and neutrophil leucocytes so that these cells' ability to destroy ingested organisms is diminished (Quie *et al.*, 1967; Segal and Peters, 1976). In the most severe forms affected boys die in infancy. Most cases of chronic granulomatous disease are not associated with McLeod phenotype (Marsh, 1978*a*, *b*). The finding that some boys lack Kx antigens on both leucocytes and red cells suggest that Kx synthesis in both these cell lines is ordered by the same, or a closely related structural gene. Linkage between the Xk and Xg blood groups was reported by Marsh (1978*b*).

The family of Case 2 is informative (*see* fig. 2) about the linkage relations of *Xg* and *Xk*. The mother is heterozygous for *Xg* because she is Xg(a+) and has Xg(a−) children and for *Xk* because she has a son with the McLeod phenotype (B1) and two sons with normal Kell groups. She has given *Xg* and X^4k to her affected son (B1), Xg^a and X^1k to one of her normal sons (B3), but *Xg* and X^1k to the other (B2). There is, therefore, at least one recombinant between the *Xg* and *Xk* loci provided that the McLeod phenotype of Case 2 (B1) is not due to mutation or to a background unrelated to *Xk*. Thus, despite the probable recombinant reported here, the *Xk* and *Xg* loci must be very close to each other.

Recombination between the Xg blood group and chronic granulomatous disease has been reported (Densen *et al.*, 1981). The Xg locus is situated near the end of the short arm of the X chromosome close to the loci for ocular albinism and ichthyosis (Race and Sanger, 1975; McKusick and Ruddle, 1977), around Xp 22.3 (Miller and Siniscalco, 1982).

Relationship of McLeod Syndrome to the X-linked Muscular Dystrophies

Since the McLeod phenotype is inherited as an X-linked recessive trait the myopathy associated with it must be considered in relation to the other X-linked neuromuscular diseases (Table 5). In the great majority of these, kindreds muscle, rather than nerves or anterior horn cells, is affected. All the X-linked myopathies, apart from that found in McLeod syndrome, are characterized by progressive muscular weakness and atrophy, although the age of onset may be delayed in some of these disorders until the second or third decade, for example, in those patients described by Mabry *et al.* (1964) and Ringel *et al.* (1977). Our two subjects with McLeod phenotype were 37 and 48 years old, respectively; neither showed clinical features of muscular disease. The cases described by Marsh *et al.* (1981) ranged from 9 to 67 years in age, and there was similarly no evident weakness in these patients. The pathological findings in the muscle biopsies of our two subjects with McLeod

TABLE 5. X-LINKED RECESSIVE MYOPATHIES

Duchenne muscular dystrophy
Becker muscular dystrophy, and similar (? related) slowly progressive X-linked myopathies (1, 2)
Emery-Dreifuss syndrome (3)
X-linked scapuloperoneal myopathy (4)
X-linked myotubular myopathy (5)
McLeod phenotype

(1) Mabry *et al.* (1965). (2) Ringel *et al.* (1977). (3) Emery and Dreifuss (1966). (4) Thomas *et al.* (1972). (5) van Wijngaarden *et al.* (1969).

phenotype differed from those of the severe forms of X-linked dystrophy, namely, Duchenne and Becker muscular dystrophies, in that there was no fibrosis and hyaline fibres were not present. Clusters of necrotic and regenerating fibres were present, however, and there was subsarcolemmal and sarcoplasmic calcium deposition in scattered, abnormal muscle fibres. In Duchenne muscular dystrophy a similar calcium deposition has been noted in abnormal fibres (Bradley and Fulthorpe, 1978; Carpenter and Karpati, 1979) and this forms part of the evidence for a membrane defect in this disease (Mokri and Engel, 1975). Transmission electron microscopic studies in the biopsies of our patients have not revealed any discontinuities in the plasma membranes of muscle fibres. Freeze-fracture ultrastructural studies of muscle fibre or red cell membranes have not yet been carried out in McLeod phenotype, but this might allow further characterization of the membrane defect presumed to be present in this condition in these two tissues. However, Wakayama *et al.* (1982) have reported their inability to confirm previous descriptions of abnormalities (Schotland *et al.*, 1977; Wakayama *et al.*, 1979) in intramembranous particle density in erythrocytes of patients with Duchenne muscular dystrophy. An association, probably fortuitous, between chronic granulomatous disease and Duchenne muscular dystrophy has been reported in a single case (Kousseff, 1981); the Kx antigenicity in this case was not described.

Studies of families of boys with Duchenne dystrophy have shown no measurable linkage with the loci for the Xg blood group (Blyth *et al.*, 1965), or the deutan colour blindness and glucose 6-phosphate dehydrogenase loci (Emery, 1966; Zatz *et al.*, 1974). Similarly, there is no detectable linkage between Duchenne muscular dystrophy and haemophilia A (Konagaya *et al.*, 1982). On the other hand, genetic studies in Becker muscular dystrophy have shown linkage with the loci for deutan colour blindness (Emery *et al.*, 1969; Zatz *et al.*, 1974), suggesting that, unlike Duchenne dystrophy, the locus for Becker dystrophy is located on the long arm of the X chromosome (*see* Addendum).

Studies of seven girls with the clinical features of Duchenne muscular dystrophy, in whom the disease was due to X-autosome translocation, have all indicated a break of the short arm of the X chromosome at the Xp21 band suggesting that the genetic locus for the disease is at or near this part of the X chromosome (Berg and Conte, 1974; Verellen *et al.*, 1977; Canki *et al.*, 1979; Lindenbaum *et al.*, 1979; Greenstein *et al.*, 1980; Jacobs *et al.*, 1981; Zatz *et al.*, 1981). Although the Xg locus is also on the short arm of the X chromosome no linkage with Duchenne dystrophy has been found. Studies of the X chromosomes of boys with Duchenne dystrophy using high resolution banding techniques have failed to show abnormalities at the Xp21 band (Spowart *et al.*, 1982). The precise locus may be definable using a cloned DNA sequence linked to the Duchenne locus (Murray *et al.*, 1982). Patients with Duchenne dystrophy show normal Kell antigenicity and therefore do not show the McLeod red cell phenotype (Marsh *et al.*, 1981); the genetic loci for McLeod phenotype and Duchenne dystrophy must therefore be separate. Similarly, the expression of Kell antigens in Becker dystrophy is normal (P. Tippett (1982) personal communication). A relation between McLeod phenotype and Duchenne muscular dystrophy might be suggested by the situation of the loci for these two disorders on the short arm of the X chromosome, since this might allow the differences in expression of the various haematological, membrane and muscle abnormalities in the different syndromes (Table 6). However, these loci are probably widely separated.

TABLE 6. COMPARISONS OF McLEOD SYNDROME AND X-LINKED MUSCULAR DYSTROPHY

McLeod phenotype	*Duchenne muscular dystrophy*	*Becker muscular dystrophy*
X-linked	X-linked	X-linked
Abnormal expression of Kell blood group antigen (1)	Normal Kell expression (1)	Normal Kell expression (2)
Raised blood CK	Very raised blood CK	Very raised blood CK
Subclinical myopathy	Severe myopathy	Moderately severe myopathy
? No cardiac involvement	Cardiomyopathy (3)	? Cardiac involvement (3)
Acanthocytes, echinocytes and anisocytes (4)	Abnormal red cell morphology including echinocytes (5, 6)	No data on red cell morphology
Increased spectrin phosphorylation in red cells (7)	Increased spectrin phosphorylation in red cells (8, 9)	Increased spectrin phosphorylation in red cells (10)

(1) Marsh *et al.* (1981). (2) P. Tippett (1982), personal communication. (3) Walton and Gardner-Medwin (1981). (4) Wimer *et al.* (1977). (5) Matheson and Howland (1974). (6) Miller *et al.* (1976). (7) Tang *et al.* (1981). (8) Roses *et al.* (1976*a*). (9) Roses *et al.* (1976*b*). (10) Roses (1977).

There is clinical evidence of genetic heterogeneity in the Duchenne muscular dystrophy phenotype (Emery, 1981). First, boys in whom the disease is associated with mental retardation experience a later age of onset than affected boys of normal intelligence (Emery *et al.*, 1979) and, secondly, there is correlation within affected families between the age of onset and the age of restriction to a wheelchair (Feingold *et al.*, 1971). Scott *et al.* (1982) have also commented that 'it is extremely difficult to define exact boundaries between the Duchenne type of muscular dystrophy and milder forms'. Genetic heterogeneity within the clinical syndrome suggests that the X chromosome locus for Duchenne muscular dystrophy involves more than a single gene.

Relationship of McLeod Phenotype to the Acanthocytic Neuromuscular Syndromes

Two major subdivisions of the acanthocytic neuromuscular syndromes have been proposed (Bruyn, 1977), abetalipoproteinaemic (Bassen and Kornzweig, 1950) and normolipoproteinaemic (Estes *et al.*, 1967). These disorders are sporadic, or inherited as autosomal recessive or dominant, rather than X-linked traits (Bruyn, 1977). The clinical features include dementia, sensorimotor neuropathy, mental retardation, seizures, cerebellar signs, tremor, choreoathetosis, retinitis pigmentosa, corticospinal signs, pes cavus and torticollis. Muscle biopsies and EMG studies in these cases have shown neurogenic muscle atrophy (Aminoff, 1972) although myopathic features, with raised blood creatine kinase levels, probably secondary in type (Schwartz *et al.*, 1976; Swash and Schwartz, 1977) have also been noted in the normolipoproteinaemic chorea-acanthocytic group (Limos *et al.*, 1982). It is interesting that Schwartz *et al.* (1982) have reported the McLeod phenotype in two cases of normolipoproteinaemic chorea-acanthocytosis syndrome. It may thus be relevant to study red cell Kx antigenicity in this group of disorders.

ADDENDUM

Since this paper was written it has become apparent that the locus for Becker's X-linked muscular dystrophy is probably also situated on the short arm of the X chromosome (Kingston H M, Thomas M J T, Pearson P L, Sarsrazi M, Harper P S (1983) Genetic linkage between Becker's muscular dystrophy and a cloned DNA sequence of the short arm of the X chromosome. *Journal of Medical Genetics*. In press.).

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FROM 4 TO FOUR

A SUPPLEMENT TO 'FROM THREE TO 3'

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SUMMARY

The psycholinguistic investigation of the ability of patients with Broca's and Wernicke's aphasia to transcode quantities from the ideographic digital coding system to alphabetical numerals parallels our previous study on the reverse transcoding task. The results support the generality of differential impairment of syntactic/nonsyntactic skills in Broca's and Wernicke's aphasia.

INTRODUCTION

In a previous study we investigated the abilities of two groups of aphasic patients to transcode integer quantities from alphabetically written forms (numerals) to Arabic digit strings (numbers) (Deloche and Seron, 1982). The one-to-one correspondence between the two coding systems, the small number of lexical primitives, the simplicity of the grammars, and the frequent occurrence of the task in everyday life for writing cheques, were why we chose this domain to investigate the pattern of dissolution of aphasic subjects' performances in transcoding tasks theoretically equivalent to translations from one language or modality to another. The results indicated that Broca's (and more particularly those subjects with agrammatism) and Wernicke's aphasics were differentially impaired in a way that paralleled the general dissociation of linguistic abilities of the two types of aphasia along the syntactic/semantic dimensions. It could thus be tentatively concluded that, despite its formal autonomy with reference to language, the alphabetical coding system for quantities and the psycholinguistic procedures of that system are not disrupted independently of the other linguistic skills. This conclusion seems at variance with classic observations according to which the reading of numbers is often preserved in alexic syndromes (Hécaen and Kremin, 1976). As indicated by Coltheart (1980), the 'number preservation' effect found with ideographically written forms (numbers) does not seem to have been systematically investigated in the alphabetical coding system. Even Hécaen and Kremin (1976) did not actually compare their aphasic patients' performances in the two scripts since only digital forms were used in their study. The results of our previous study seemed to support the hypothesis of a general disorder affecting the manipulation of hierarchical structures *per se* in

Broca's aphasics, that is, the structures that underlie the arrangement of words in sentences, the arrangement of lexical primitives in numeral forms, or the organization of branches and nodes in trees as reported by Grossman (1980).

In the present study, we are concerned with the ability of Broca's and Wernicke's aphasics to transcode integer quantities from the digital to the alphabetical system. This task is the reverse of that used in our previous study but, given the peculiarities of the coding systems and particularly the differences of serial ordering constraints, the two tasks are far from being simple inverses of each other, as has been shown by Power and Longuet-Higgins (1978), who developed transcoding algorithms in the two directions. The present paper continues our previous study by analysing the subjects' performance when handling a task that involves different psycholinguistic procedures that cannot be simply inverted and that operate on essentially different material, namely, ideographic *versus* alphabetical scripts (*see* Besner and Coltheart, 1979, for the relevance of this distinction).

In both studies, the subjects' responses, either correct or erroneous, are considered to be produced by neurolinguistic mechanisms whose procedures belong to the normal cognitive system. Our interest is mainly in the disorganization of the set of psycholinguistic procedures, their overgeneralization, and their individual degeneration. In both studies, too, the pattern of dissolution of Broca's and Wernicke's aphasics is tentatively related to the differential syntactic/semantic impairment classically reported in the two types of aphasia. Finally, in both studies, the notion of procedures operating on stack-like structures is considered relevant to the study of how integer quantities are processed in transcoding tasks. In stack structures, elements are defined along two independent dimensions, the stack (a one-dimensional array) to which they belong and their position within that stack. Three stacks were considered: the units stack containing the nine digit names from 'UN' (one) to 'NEUF' (nine); the 'particulars' stack containing the six one-word numerals from 'ONZE' (eleven) to 'SEIZE' (sixteen); and the 'tens' stack containing 'DIX' (ten), 'VINGT' (twenty), etc.

MATERIALS AND METHODS

The subjects were the same 14 aphasic patients who participated in our previous study. There were 7 Wernicke's and 7 Broca's aphasics (including two agrammatic subjects). The subjects wrote the numeral forms of 100 written numbers referring to the same quantities as in the former study, after at least a two-week interval. The instructions stressed that each digit form was to be considered as a whole representing an amount of something like money or distance and that the subject's task was to write the corresponding form in the alphabetical coding system.

RESULTS

Analysis of Erroneous Transcriptions: Global Data

The data corpus consisted of 1,400 transcriptions produced by 14 aphasic subjects for the 100 items of the test battery; no items were omitted. Orthographic errors that did not change the phonemic reading of the numeral lexicon elements, such as 'CINQUE' for 'CINQ' (5), were not registered as errors, nor was the incorrect use of the letter 'S' indicating the plural in some numeral lexicon elements. The omission of the symbol '-' (hyphen) between some elements or the presence of monetary indications ('Francs' or 'Frs') were also not considered errors.

With these conventions, 378 transcriptions were incorrect (mean frequency: 0.27). The Broca's aphasics committed 246 errors and the Wernicke's only 132. Twelve numbers were correctly transcoded by all the subjects, among them 10 lexical primitives. The error frequency for the transcriptions of one-word numerals was 0.02 (2/126) for units, 0.13 (11/84) for simple tens (one-word tens names), but 0.26 (22/84) for particulars. It was 0.38 (16/42) for composed tens (two- or three-word tens names). Since the two groups of patients were not equivalent in terms of a criterion of severity of aphasia, the question of possible double dissociation of the subjects' performances by type of aphasia and one or another material dimension will be investigated by considering the relative proportions of different types of errors within the two groups. No severity effect was found in our previous study, the error frequencies for transcoding numerals into numbers being 0.21 for the same 7 Broca's aphasics and 0.18 for the same 7 Wernicke's aphasics (Deloche and Seron, 1982).

Qualitative Analysis

We distinguish three sources of errors in relation to the cognitive processes: errors committed during the recognition of the digits and/or the production of their numeral name, serial ordering errors in parsing from left to right in the digit string, and errors in the transcoding process itself.

Digit recognition and numeral lexicon production errors. Verbal, literal, phonemic, morphemic and neologistic paragraphias. This set contains the 23 erroneous transcriptions where one letter string at least was alien to the numeral lexicon. The sequence of letters may be a word (verbal paragraphia) or not, and it may or may not share most of its units with the correct form at some level (letters, phonemes, morphemes, or neologisms). The Broca's aphasics produced 19 such errors, and one Wernicke's aphasic was responsible for the remaining 4. In one case, this subject made a verbal literal paragraphia: '200' (DEUX CENTS) → 'DEUX CENTRE' (two centre). In 3 other cases, the errors were neologistic as in '71' (SOIXANTE ET ONZE) → 'SEPTON ONZE'. The small number of neologistic productions in the corpus is probably due to two biases: first, low-level literal paragraphia was a selection criterion; second, orthographic errors were ignored when scoring the subjects' productions. This small number must not, consequently, be viewed as a significant sample of a random set of numeral writing of aphasic subjects. The erroneous transcriptions by the Broca's aphasics were of another nature in that they were essentially morphemic or verbal paragraphias referring to quantities. Verbal paragraphias were sometimes numeral adjectives such as 'NEUVIEME' (ninth) in '97' (QUATRE-VINGT-DIX-SEPT) → 'NEUVIEME

SEPT', but more frequently nouns such as 'DOUZAINE' (dozen) in '112' (CENT DOUZE) → 'CENT DOUZAINE'. Morphemic paragraphias generally resulted from incorrect suffixation of digit names either because it was not the appropriate bound morpheme or because it required a previous modification of the digit name. For example, '45' (QUARANTE-CINQ) was erroneously transcribed as 'QUATRANTE CINQ' with 'QUATRE' (4) in the tens position becoming 'QUATR' + 'ANTE', which is the generalization of a procedure that leads to the correct result with other tens names. We stress that the information relative to the stack position was always preserved in all the errors by the Broca's aphasics. They never produced verbal paragraphias on digit names.

Stack errors. A stack error, such as '60' (SOIXANTE) → 'SIX' (6), is identified in a numeral sequence that differs from the correct sequence only in that one element of the erroneous production preserves the information regarding the position within the stack (6th) but not that relative to the stack itself (units for tens). There were 18 errors of this type: 10 by the Wernicke's aphasics and 8 by the Broca's. There was a tendency in the Broca's group to produce errors by replacing particulars or tens names by a unit in the numeral—6 out of 8 errors were of this sort—and the Broca's aphasics never committed a stack error on a numeral unit name. The two remaining errors consisted of confusing tens and particulars suffixes (-ANTE and -ZE, respectively). Stack errors committed by the Wernicke's aphasics were less regular and, in two cases, concerned unit names.

Stack position errors. In this case the processing of the information relative to the position in the stack is disturbed, the stack information being preserved: '106002' (CENT SIX MILLE DEUX) → 'CENT TROIS MILLE DEUX' (103002). In 6 erroneous transcriptions the only error was of this type (4 produced by Wernicke's and 2 by Broca's aphasics).

Serial ordering errors. Aborted transcriptions. In 11 cases the transcriptions were aborted. This occurred either with composed tens like '97' (QUATRE-VINGT-DIX-SEPT) → 'NEUF' (9); or with numbers like '943' (NEUF CENT QUARANTE-TROIS) with 'CENT' (hundred) needed as a multiplicand; or in digit strings containing at least one '0': '1016' (MILLE SEIZE) → 'MILLE'. The Broca's aphasics produced 10 out of the 11 such errors. This might be due to the subjects' awareness that they had just failed or were about to fail in transcribing the items. In such a situation, they might prefer to stop the transcription. Conversely, the lack of such knowledge on the part of the Wernicke's aphasics might account for their very small number of aborted transcriptions.

Numeral displacements. We define numeral displacement as an erroneous transcription composed of the same individual numeral elements as the correct writing but sequenced in a different way. There were 16 errors of this type, all committed by the Broca's aphasics. It must be pointed out that the erroneous serial ordering of numeral lexicon elements did not deviate randomly from the correct sequencing. In 15 cases, the errors seemed systematic and consisted of inverting the relative positions of the multiplicand and the multiplier, the former being erroneously placed before the latter, as in '27419' (VINGT-SEPT MILLE QUATRE CENT DIX-NEUF) → 'MILLE VINGT SEPT CENT QUATRE DIX NEUF'.

Transcoding errors. All the errors listed under the heading of transcoding errors presuppose that each isolated digit element in the number string has been correctly identified, that the digit string was processed from left to right in sequence, and that there was no disturbance of the serial organization of numeral lexicon elements when producing the response.

Metalinguistic descriptions. In 7 cases, the subjects' productions were a metalinguistic description rather than a true numeral transcription. In such cases, the transcriptions described either the digit string: '106002' (CENT SIX MILLE DEUX) → 'CENT SIX 2 ZERO DEUX', where '2 ZERO' stands for 'two times digit 0', or an element of the numeral: '71' (SOIXANTE ET ONZE) → 'SOIXANTE ET UN UN' stands for 'ONZE' (11) for two occurrences of the digit '1' (UN). All such productions came from the Wernicke's aphasics.

Term-by-term strategy. The errors in this category resulted from the very elementary transcoding strategy that consisted of writing each individual digit—including '0'—by its digit name, from left to right, for example, in '4003' (QUATRE MILLE TROIS) → 'QUATRE ZERO ZERO TROIS'. There were 40 errors of this type, with 35 of them being produced by the Broca's aphasics. While no such errors occurred with composed tens in the group of Wernicke's aphasics, the Broca's aphasics committed 18 out of the 35 erroneous transcriptions on composed tens like '97' (QUATRE-VINGT-DIX-SEPT) → 'NEUF SEPT' or '80' (QUATRE-VINGTS) → 'HUIT ZERO'. This result and the fact that the two agrammatic subjects were responsible for 28 out of the 35 errors in the group of Broca's aphasics seem to support the hypothesis that the term-by-term transcoding strategy corresponds to a general syntactical disorder. Although this strategy might look functionally very much like the letter-by-letter reading found in some dyslexic syndromes, it should be noted that the agrammatic subjects who produced the highest proportion of the erroneous term-by-term transcoding of digit strings were not able to read out individual letters. Finally, non-French-speaking readers of this paper should note that this strategy is by no means natural for French-speaking subjects, since even telephone numbers are parsed into digit substrings of two or three digits, each substring being coded into the corresponding numeral. For instance, the phone number for the Salpêtrière Hospital in Paris (5841412) would be given as 'CINQ CENT QUATRE-VINGT QUATRE' (584) 'QUATORZE' (14) 'DOUZE' (12) and not 'CINQ HUIT QUATRE UN QUATRE UN DEUX'.

Term-by-term strategy when '1' is at the beginning of the number. The errors in this category seem to have resulted from a transcoding strategy similar to the simple term-by-term strategy except that the first digit of the number string is a '1' that is not transcoded by its digit name 'UN' (1) but by 'MILLE' (thousand), 'CENT' (hundred), or 'DIX' (10). There were 52 errors of this kind, 12 committed by the Wernicke's aphasics and 40 by the Broca's aphasics. The first digit was generally transcoded properly by the Wernicke's aphasics (11 cases out of 12), but only 9 times out of the 35 erroneous transcriptions produced by the two Broca's aphasics with agrammatism. One transcribed the first digit '1' by 'CENT' (hundred) whatever the digit string length (except particulars where the first digit '1' was transcoded by 'DIX' (10)). For this subject, the erroneous transcriptions may have resulted from an overgeneralization of transcoding strategies correct in other contexts: '1' is in fact 'CENT' in the hundreds position as in '153' (CENT CINQUANTE-TROIS) and transcoding '1' in the tens position by the tens name 'DIX' (10) is correct when followed by '0', '7', '8' and '9' but not in '112' (CENT DOUZE) → 'CENT DIX DEUX'. In the same way, the other agrammatic subject generalized the transcoding of '1' in the thousands position by 'MILLE' to the case of six-digit numbers.

Erroneous lexical transcription of the digit '1' in the hundreds or the thousands position. As a rule, the digits in the hundreds and thousands positions must be transcribed by their digit name followed by 'CENT' (hundred) and 'MILLE' (thousand), respectively. Apart from the case of '0', which is never transcribed by its digit name 'ZERO', the only exception to this rule is the digit '1' itself for which the digit name 'UN' (1) must not be written before 'CENT' or 'MILLE'. In 17 erroneous transcriptions, the only error resulted from the violation of this exception, the general rule being applied to produce, for example, 'UN MILLE UN CENT DEUX' instead of 'MILLE CENT DEUX' (1102). Wernicke's aphasics were responsible for 13 out of 17 such errors. This would not be an error in the English numeral system. Unlike the English numeral system, the French for '1214' is read 'MILLE DEUX CENT QUATORZE' and not 'UN MILLE DEUX CENT QUATORZE' (ONE THOUSAND . . .).

Omission of syntactical elements in the numeral string. Depending on their positions in the number string, individual digits may be transcribed into one or several elements in the corresponding numeral form. The latter occurs with 'CENT' (hundred) and 'MILLE' (thousand) when multiplicands, with the composed tens, and with the operator 'ET' (and). Multiplicand omissions accounted for 30 erroneous transcriptions, for example, '857' (HUIT CENT CINQUANTE-SEPT) → 'HUIT CINQUANTE SEPT', '83' (QUATRE-VINGT-TROIS) → 'QUATRE TROIS'. The Broca's aphasics produced 17 out of the 30 such errors. The omissions of the additive constant 'DIX' (10) in composed tens accounted for 14 erroneous transcriptions (7 from each subject group). The productions were thus syntactically well-formed numerals, but they indicated quantities that were 10 less than the original number. In the simplest cases, 'DIX' (10) was simply omitted as in '97' (QUATRE-VINGT-DIX-SEPT) → 'QUATRE VINGT SEPT' (87). In other cases, neither 'DIX' nor the particular were produced but the digit name appeared as in '75' (SOIXANTE-QUINZE) → 'SOIXANTE CINQ' (65). In 3 cases, the erroneous transcriptions differed from the correct numeral only in the omission of 'QUATRE' (4) as multiplier in composed tens names, as in '91' (QUATRE-VINGT-ONZE) → 'VINGT ONZE' or '80' (QUATRE-VINGTS) → 'VINGT'. Two such errors were produced by the Broca's aphasics. There were 12 transcriptions with errors consisting only of the omission of the arithmetical operator 'ET' (and). Seven such errors were produced by the Broca's aphasics, such as '51' (CINQUANTE ET UN) → 'CINQUANTE UN' or '71' (SOIXANTE ET ONZE) → 'SOIXANTE ONZE'.

Mixed errors. There were 82 erroneous productions that could be interpreted either as the result of the combination of two erroneous transcoding strategies discussed above or in terms of one or the other strategy. Thus, the transcription 'TROIS DEUX' instead of 'TROIS CENT VINGT' (320) may be either the result of transcoding each digit into its digit name ('3' → 'TROIS' and '2' → 'DEUX') but without violating the rule that '0' is never transcribed by 'ZERO', or by the omission of 'CENT' (hundred) when a multiplicand and a stack error with '2' in the tens position being transcribed as 'DEUX' (2) instead of 'VINGT' (20). Such erroneous transcriptions have been included in the 'mixed errors' category but, in most of the cases, inspection of the most frequently used transcoding strategy by the particular aphasic subject permits a choice between the different interpretations with confidence. The combination of several sources of error is evidenced in cases like '857' (HUIT CENT CINQUANTE-SEPT) → 'HUIT QUATRE SEPT', which is obtained by transcribing each digit into its digit name ('857' → 'HUIT CINQ SEPT') and by a stack position error for one digit name ('QUATRE' (4) instead of 'CINQ' (5)); in '3082' 'TROIS MILLE QUATRE-VINGT-DEUX) → 'TROIS ZERO QUATRE DEUX', the same transcoding strategy (digit → digit name) was applied to three out of the four digits ('3', '0', '2') whereas '8' in the tens position was correctly transcribed except for the omission of the multiplicand 'VINGT' (20): '8' → 'QUATRE' (4) instead of 'QUATRE-VINGTS'. The transcription of '70' (SOIXANTE-DIX) by 'SEIZE' (16) combined the omission of the additive constant 'DIX' (10) by '70' → 'SOIXANTE' (60) and a stack error: transcribing the '60' by the corresponding particular 'SEIZE' (16). In some cases, the erroneous transcriptions contained two productions delivered by different transcoding strategies for the same digit in the numbers. For example, '3216' (TROIS MILLE DEUX CENT SEIZE) → 'TROIS MILLE DEUX UN SEIZE' resulted from the omission of the multiplicand 'CENT' (hundred) and from two transcodings of '1' in the tens position, first by its digit name 'UN' (1) then by the particular 'SEIZE' (16). The Broca's aphasics produced 46 out of the 82 mixed errors.

Miscellaneous errors. In this category, we placed the erroneous transcriptions that are not of the types listed in the preceding sections. They were not numerous: 47 out of 378 or 12.4 per cent. Yet careful examination of some miscellaneous errors indicates that they probably resulted from disorders not clearly identifiable because they rarely occurred in isolation in other parts of the data. A different type of analysis of subjects' productions would, of course, have removed all 'unclassified errors'. A taxonomic description of erroneous transcriptions, considered as serial ordering errors combining additions, omissions, and displacements of lexical primitives would have led to an exhaustive analysis of the data. But in this approach, the following sophisticated miscellaneous error '90' (QUATRE-VINGT-DIX) → 'QUINZE UN ZERO' would be accounted for by suggesting that it was the result of the successive omissions of 'QUATRE' (4), 'VINGT' (20), and 'DIX' (10) and the substitution of 'QUINZE' (15), 'UN' (1), and 'ZERO' (0), respectively. Such *ad hoc* analysis is of little value since it is only a description of what is present and what is absent in the erroneous transcriptions and has no relationship to the subprocesses implied in the transcoding production task. Moreover, it cannot explain why systematic erroneous transcriptions occur in particular contexts.

CONCLUSIONS

As indicated in the Table by the distributions of erroneous transcriptions according to the different error sources, some factors clearly emerge that differentially affected the performances of the two groups of aphasic subjects.

The group of 7 Broca's aphasics produced more erroneous transcriptions than the 7 Wernicke's, the ratio being 1.9 to 1. Further analyses will indicate that the two groups do indeed differ qualitatively as demonstrated by double dissociations and error distributions departing from the global ratio. First, however, some factors must be mentioned that might have biased the ratio in one direction or the other. The two groups were not random samples of aphasic patients since severe Wernicke's aphasics, who produce numerous paragraphias, were excluded from the study, and there were two agrammatic subjects among the Broca's aphasics. The test

TABLE DISTRIBUTION OF ERRORS BY TYPE IN EACH APHASIC GROUP

	Subjects		
Type of error	*Broca's aphasics* (n = 7)	*Wernicke's aphasics* (n = 7)	*Total* (n = 14)
Paragraphias	19	4	23
Stack errors	8	10	18
Stack position errors	2	4	6
Aborted transcriptions	10	1	11
Numeral displacements	16	—	16
Metalinguistic descriptions	—	7	7
Term-by-term strategy	35	5	40
Partial term-by-term strategy with leftwards '1'	40	12	52
Undue transcription of '1' in thousands/hundreds positions	4	13	17
Omission of syntactical elements			
Multiplicands	17	13	30
Additive constant '10'	7	7	14
Multiplier '4'	2	1	3
'ET'	7	5	12
Mixed errors	46	36	82
Miscellaneous	33	14	47
Total	246	132	378

battery may also have been biased in that types of items that present more difficulty for one group than for the other may have been over-represented.

Most of the erroneous transcriptions of Broca's aphasics seemed to result from grammatical (nonlexical) difficulties as indicated on the morphological and syntactical levels. Their verbal or morphemic paragraphias belonging to the domain of quantities, their stack errors being orientated toward the units names stack, and the very few cases of position-within-stack errors clearly demonstrated that the individual digits in the number string were correctly identified. These errors may have been the result either of morphological difficulties in constructing composed (root + bound morpheme) numeral names or of syntactical impairments in parsing the digit string into hundreds, tens, and units. The nature of the errors may tentatively favour the first hypothesis. The syntactical difficulties of Broca's aphasics were evidenced at the production level in the numeral displacement errors where multiplier and multiplicand were systematically reversed, thus leading to numeral element strings where the syntactical ambiguities (thousand, hundred) were assigned their lexical (nonmultiplicand) role (*see* Andreewsky and Seron, 1975, for similar findings in the performance of an agrammatic patient reading aloud isolated words and sentences). Errors involving omissions of syntactical elements (multiplicands, multipliers, and additive constants in composed tens, and the operator 'and') were essentially committed by Broca's aphasics (191/267). The term-by-term transcoding strategy also differentiated the two groups of subjects since such errors occurred 7 times more often among the Broca's than among the Wernicke's aphasics, particularly in syntactically difficult contexts (composed tens and digit strings ending with '1', thus requiring the operator 'and').

The sources of errors in the cases of Wernicke's aphasics were less clear. The small number of aborted transcriptions and the metalinguistic descriptions may reflect the lack of nosognosis of such patients and their difficulty in inhibiting their responses. The stack position errors and the nondirectional stack errors seem likely to reflect impairments that parallel their semantic confusions in linguistic tasks. At the syntactical level, it should be stressed that Wernicke's aphasics used the term-by-term transcoding strategy less frequently than did the Broca's aphasics (and not necessarily in complex syntactical contexts) and that their erroneous productions were more often well-formed numerals (16/115) than those of the Broca's (9/211).

The differential abilities of Broca's and Wernicke's aphasics in transcoding quantities from the ideographic digital code into the alphabetical system thus seem to parallel the results of the reverse transcoding task and the classical double dissociation between the syntactic/semantic skills of the two groups of patients.

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PERIPHERAL PROJECTIONS OF FASCICLES IN THE HUMAN MEDIAN NERVE

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SUMMARY

Intraneural microstimulation combined with microneurography was employed to study the degree of mixing of muscle and skin nerve fibres at two levels in the human median nerve, and to delineate the area of skin supplied by a fascicle. It was found that about half the fascicles at upper arm level appeared to supply exclusively skin or muscle, while the remainder were considerably committed to one or the other. Further, the projection territories of skin nerve fascicles, both at the wrist and in the arm, tended to be discrete, confluent areas covering no more than 20 per cent of the median nerve territory. At the wrist fascicular territories usually resembled the innervation area of a single palmar digital nerve while in the upper arm they tended to cover a digital interspace. These findings suggest that most of the rearrangements of spinal root fibres into terminal nerve branch groupings occur at brachial plexus level, while the intraneural fascicular plexus may act as a safety mechanism allowing for nondermatomal overlap at proximal levels.

INTRODUCTION

Study of the topographic anatomy of peripheral nerves has been relatively neglected since Sunderland's original work (1945) on the 'intraneural topography' of the radial, median and ulnar nerves in man. By examining serial histological sections of peripheral nerves obtained at autopsy he was able to demonstrate the presence of an intricate fascicular plexus throughout the length of the nerve. Even though he admitted that with his method the course of individual nerve fibres could not be followed, it was his view that the complexity of fascicular rearrangements was such that it 'excluded the possibility of groups of fibres being confined throughout their course to a particular funiculus'. His conclusions have never been challenged and, indeed, most contemporary textbooks imply a degree of transfascicular intermingling such that any proximal fascicle would contain fibres randomly dispersed in several distal fascicles and thus projecting throughout the total cutaneous and muscular territory of the nerve. In fact, surprisingly little is known about the degree of segregation of cutaneous as opposed to muscle nerve fascicles along their course in mixed nerve trunks, or about the peripheral projection territory of the complement of cutaneous nerve fibres contained in a fascicle.

Modern neuroanatomical tracing techniques are unsuitable for human studies but an indirect physiological method can be applied to explore these questions. Since intraneural microstimulation (INMS) with Vallbo-Hagbarth semimicroelectrodes may be used to activate single nerve fibres in alert humans (Torebjörk and Ochoa, 1980) or, as will be shown here, to recruit bundles of them or the whole fibre complement within a nerve fascicle, it becomes possible to take advantage of the localizing capacity of the brain to map the cutaneous projection of individual sensory fibres or of groups of them at any point along the course of a nerve. We have applied this method to study (1) the degree of segregation of cutaneous and muscle fascicles in mixed nerves and (2), the distribution within the total cutaneous nerve territory of the peripheral projections of the fibre complement of nerve fascicles.

METHODS

Experimental Procedure

Sixty-six experiments were carried out on the median nerves of 4 healthy adults, 3 male and 1 female, whose ages ranged from 20 to 44 years. Sixteen experiments were performed at the wrist (1 to 2 cm proximal to the radiocarpal joint) and 50 at various levels in the upper arm (5 to 13 cm proximal to the medial humeral epicondyle). The subjects were asked to describe the quality and to map the location of any sensory experience evoked by INMS. Tungsten semimicroelectrodes were used with an uninsulated tip 50 to 180 μm long and a tip diameter in the order of 5 to 15 μm. A Grass S48 constant voltage stimulator with stimulus isolation unit delivered square wave pulses of 0.25 ms duration at an amplitude of 0.3 V and a frequency of 5 Hz during electrode insertion. The range of voltages used during the experiments was 0.1 to 4 V corresponding to currents of up to 130 μA, assuming an electrode impedance of 30 to 100 kΩ (Hagbarth, *et al.*, 1970). Recording and display systems were as described in previous reports (Vallbo and Hagbarth, 1968; Hagbarth *et al.*, 1970).

Immediately after insertion through the skin, the electrode was advanced in the direction of the nerve while stimulating, until the subject reported sensations projected to the hand or muscle contraction was observed. When it was established that the electrode was in a stable intrafascicular position, that is, when the subject reported consistent sensations at low thresholds (usually below 0.3 V), the stimulus amplitude was returned to zero and then gradually increased to the liminal point for conscious detection. The field of projection of the first sensation was mapped by the subject on actual-size photographs of his hand. Further rises in stimulus amplitude led to the appearance of other circumscribed sensations, whose projected fields were also mapped. Such discrete sensations of distinct quality and monofocal cutaneous projection are termed 'elementary sensations' (Ochoa and Torebjörk, 1983). This process of recruitment was continued until the evoked sensations became unbearable or until a ceiling of 4 V was reached. When a visible twitch revealed that motor units were being activated, threshold was determined and an attempt was made to establish which muscle was involved.

Measurement of Areas

The margins of projected fields of sensation were traced on to a digitizer and fed into an Apple Europlus computer for calculation of areas. The median nerve territory, as seen two-dimensionally on a photograph of the palmar aspect of the hand, was determined by tracing and superimposing the projected fields of all sensations evoked in one subject in the course of the 35 experiments in which he was involved.

The statistical significance of differences between population samples was determined by means of one-way analysis of variance.

Double Electrode Experiments

Two pairs of electrodes were used in 4 experiments, 2 in the ulnar nerve in the lower forearm, and 2 in the superficial peroneal nerve above the ankle. The aim was to insert a recording electrode in the same nerve as the stimulating electrode at a point 4 to 8 cm proximal to it. In 3 instances recording and stimulating electrodes lay in different fascicles, while in the fourth experiment it was possible to place both electrodes in the same fascicle. The following were used as guidelines to recognize entry and exit from a fascicle: evoked sensations were often reported immediately upon entry; multiunit recording was always possible from within a fascicle but was lost upon exit (Hagbarth *et al.*, 1970); lastly, the threshold for the first sensation evoked by INMS was on average 0.23 V when stimulating within a fascicle and usually over tenfold higher when stimulating from outside.

The two electrodes used in these experiments were taken to be lying in different fascicles if (1) the receptive fields of multiunit responses recorded with them were different, and (2), the maximal projection territories of sensations evoked by stimulating intraneurally were separate and non-overlapping. Conversely, the electrodes were understood to be lying in the same fascicle if the receptive fields of multiunit responses coincided and maximal projection territories were identical. In either case, electrical pulses of the same characteristics as above were delivered through the distal electrode while the proximal electrode was used for recording. Propagated neural activity at the proximal site was monitored on consecutive oscilloscope sweeps triggered by the stimulus artefact.

RESULTS

Intraneural microstimulation (INMS) at liminal intensities for conscious detection gave rise to an elementary sensation projected to a small, well-defined field. This is thought to be the result of activation of a single sensory unit (Torebjörk and Ochoa, 1980; Vallbo, 1981; Ochoa and Torebjörk, 1983). Increasing the amplitude of electrical stimulation did not affect the intensity of this initial sensation, but led to the sequential recruitment of new, qualitatively different sensations in a saltatory manner. The spatial projections of these elementary sensations have been described eleswhere (Schady *et al.*, 1983). After about half a dozen such elementary sensations had been recruited, qualities and fields of projection began to fuse into a compound and usually confluent sensation akin to an electric shock. Its magnitude and projected field increased with further rises in stimulus amplitude until a point of saturation was reached, beyond which no changes occurred up to stimulus amplitudes of 4 V. This was taken to represent activation of all or most of the fibres within one nerve fascicle.

Double Electrode Experiments

Three double electrode experiments were done to establish whether stimulus spread remained confined to one fascicle at the stimulus intensities used. Recording and stimulating electrodes were positioned in *different* fascicles and electrical pulses of up to 4 V were delivered through the distal electrode. No propagated activity could be detected in the nonaveraged neurogram by the proximal electrode in any of these experiments. Although there is of course no means of knowing whether there was any stimulus spread to fascicles other than the one from which the recording was being made, the results suggest that, if it occurred, it is unlikely to have been substantial.

In the fourth double electrode experiment recording and stimulating electrodes were positioned in the *same* fascicle of the superficial peroneal nerve at a distance of 4.5 cm from each other. Fig. 1 shows several superimposed compound action potentials (CAPs) recorded with the proximal set of electrodes at various stimulus amplitudes. By 0.65 V, the early A fibre components of the CAP (fig. 1A), representing activation of myelinated fibres, were virtually saturated. The amplitude of the late C fibre components continued to increase up to a stimulus amplitude of 4 V (fig. 1C), beyond which no substantial recruitment of fibres occurred up to 10 V (fig. 1D). This paralleled the levelling-off by around 4 V of the estimated magnitude of the painful electric sensation evoked in the subject. Stimulus frequencies used were 30 Hz while studying early CAP components, but only 0.3 Hz when studying late CAP components to avoid depression of C fibre excitability.

Segregation of Skin and Muscle Nerve Fascicles

INMS combined with conventional microneurography revealed the existence of four types of nerve fascicles: those supplying skin, those supplying muscle, and mixed fascicles supplying predominantly either skin or muscle.

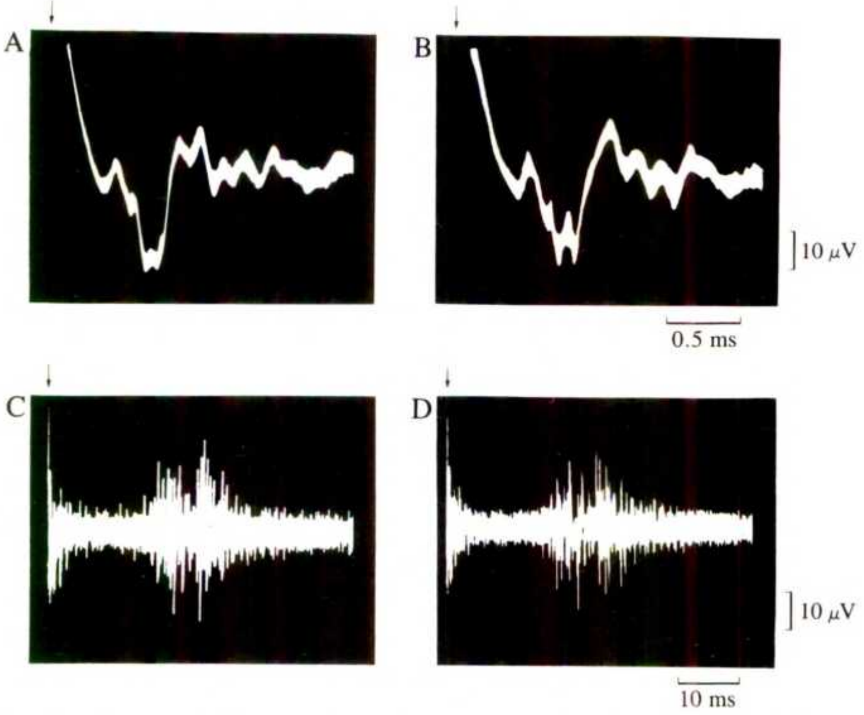


FIG. 1. Superimposed compound action potentials evoked by electrical stimulation within a fascicle and recorded with a second set of electrodes lying 4.5 cm proximally in the same fascicle. Arrows indicate stimulus onset. A, early A components of the CAP (conduction velocity 75 to 25 m/s) at a stimulus amplitude of 0.65 V. B, early components of the CAP at 4 V. C, late C fibre components of the CAP (conduction velocity 1.7 to 0.9 m/s) at 4 V. D, C fibre response at 10 V. Note that the configuration of the CAP is virtually the same between A and B and between C and D, indicating saturation of the A components by 0.65 V and of the C components by 4 V.

1. Electrical stimulation in certain fascicles evoked sensations of various qualities (tapping, pressure, dull or sharp pain, itch) projected only to the skin. There was no muscle twitch. On recording, afferent activity could be triggered only by natural stimulation of the skin, and C sympathetic discharges, when identified, had the typical features seen in skin nerve fascicles (Hagbarth *et al.*, 1972). This pattern was observed in 31 experiments, 10 at the wrist (62.5 per cent) and 21 at upper arm level (42 per cent).

2. Stimulation within other fascicles evoked predominantly cutaneous sensations, but also a minor degree of muscle twitching and/or typical cramp-like muscle pain (Ochoa and Torebjörk, 1981). This occurred in 4 experiments at wrist level (25 per cent) and 18 in the upper arm (36 per cent). The first sensation was projected to the skin in all but 3 cases, where either forearm muscle pain or, in one case, a visible muscle twitch preceded cutaneous sensations. Recording characteristics were as for (1).

3. In 2 instances, when stimulating in the upper arm (4 per cent), INMS evoked sensations projected only to muscle bellies or tendons, either as a dull cramp-like pain or, more infrequently, deep tension. Sooner or later muscle twitching occurred. On recording, afferent activity could be triggered by stretching muscle or tapping tendons, and multiunit motor neuron activity could be recorded intraneurally on voluntary activation of the appropriate muscles.

4. In the remaining experiments—2 at the wrist (12.5 per cent) and 9 in the upper arm (18 per cent)—INMS resulted predominantly in muscle twitching but some cutaneous sensations were also evoked, usually isolated and projected to widely scattered locations in the hand. Recording was dominated by muscle afferent activity and efferent sympathetic discharges, when identified, were pulse-synchronous and typical of muscle nerve fascicles (Delius *et al.*, 1972). In 5 of these experiments, less than 3 elementary cutaneous sensations were felt amidst massive motor unit recruitment.

The highest proportion of 'pure' skin nerve fascicles was obtained during early experiments, when stimulus amplitudes often did not exceed 1 V. If these early experiments are excluded, on the assumption that beyond 1 V some motor units might have been recruited, the relative proportion of strictly pure skin fascicles drops to 50 per cent at the wrist and 21.6 per cent in the upper arm.

When stimulating mixed nerve fascicles certain recurring associations were observed. At the wrist there was always some degree of muscle twitching in the thenar eminence when sensations were projected to the lateral aspect of the thumb. At upper arm level, flexion of the distal phalanx of the thumb was usually linked to flexion of index and middle fingers (5 experiments), indicating combined activation of muscles supplied by the anterior interosseus nerve. Associated cutaneous sensations were projected either to the second or the third digital interspaces. Wrist flexion and pronation also occurred jointly. Ring and middle finger flexion was usually associated with cutaneous sensations projected to the third interspace (3 experiments).

Territories of Cutaneous Fascicles

After identifying on average 5 individual elementary sensations, subjects reported fusion of qualities and projected fields with further increases in stimulus amplitude. A point of saturation was usually reached at amplitudes between 2 to 3 V. Increases of 1 V or more beyond this point caused no appreciable change in the maximal projection territory (MPT), although sometimes the magnitude of the compound sensation, felt as a tense painful throbbing, would continue to grow. The MPT was taken to represent the area of skin supplied by the fascicle containing the electrode tip.

Slightly advancing or withdrawing the electrode did not usually alter the MPT. Larger electrode displacements, however, would result either in inability to elicit a sensation by INMS, or in the appearance of a new recording and stimulation profile with an entirely different MPT. It was sometimes possible to place the electrode within the same fascicle more than once in the course of an experiment. This was judged to be the case if MPTs coincided exactly, even if individually identified sensations were not the same. In one revealing example, intraneural stimulation evoked sensations projected to the second digital interspace. When the electrode was withdrawn or advanced a few millimetres all sensation was abolished, but it reappeared with identical cutaneous projection when the electrode tip was returned to its original position.

Successive elementary sensations recruited in the course of any given experiment were on average separated by 4 to 5 cm when stimulating at the wrist, and by about 8 cm when stimulating in the upper arm (Schady *et al.*, 1983). Nevertheless, they were not scattered over the whole of the median nerve territory but were mostly contained within the innervation territory of one or two digital nerves. Similarly, at maximum stimulus amplitudes, the MPT was limited to a relatively small portion of the hand. This applied to experiments performed in the upper arm as well as at the wrist, although in the former the MPT was significantly larger.

Stimulation at the wrist. Eighty-nine per cent of elementary sensations evoked from skin nerve fascicles were projected to points lying within the territory of a single palmar digital nerve. In other words, they remained clustered down one half of the palmar aspect of a finger (figs. 2A–C). The rest were projected to a neighbouring finger (fig. 2D). No sensations, in the course of an experiment, were ever projected outside the innervation territory of more than two digital nerves. At high stimulus intensities the MPT was equally confined to one half of one finger (9 experiments) or adjacent halves of neighbouring fingers (5 experiments). The fingers and digital interspaces concerned are shown in fig. 3. It can be seen that most experiments involved fascicles supplying the thumb (8 out of 14) or index (6 out of 14). This can be accounted for by the fact that the medial half of the nerve, which at this level is still topographically arranged (Sunderland, 1945), is usually less accessible under the tendons of palmaris and flexor digitorum muscles.

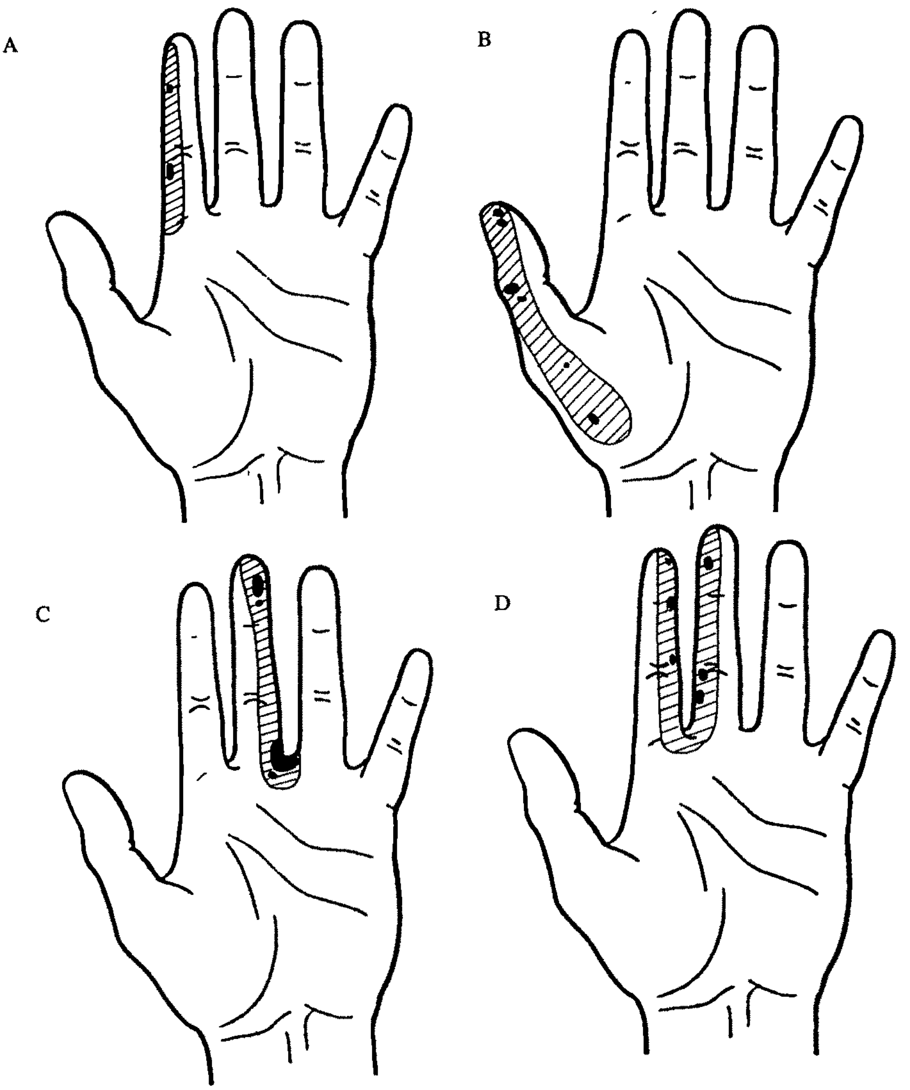
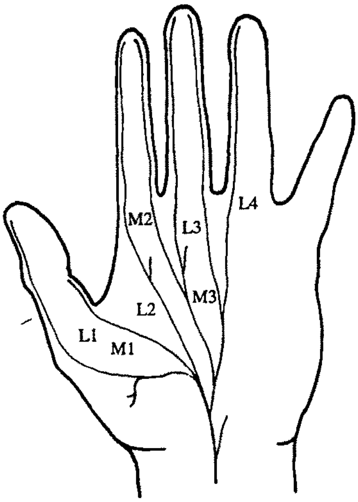


FIG. 2. Maps of projections of elementary sensations (filled-in areas), and of maximal projection territories (hatched areas) when stimulating at the wrist. Four representative examples are given. Sensations were invariably confined to one half of one finger (A, B and C) or adjacent halves of neighbouring fingers (D).

The mean area of MPTs when stimulating at the wrist was 12.8 cm.^{2} However, since the size of the subjects' hands varied considerably, it would be more appropriate to estimate the size of MPTs relative to the area of glabrous skin supplied by the median nerve. The latter was established by superimposing and pooling the MPTs obtained in the 35 experiments performed in one subject. The median nerve territory was found to be limited by a line drawn down the middle of the ring finger and extended to the ulnarmost point of the flexor tendon mass at the



	Wrist	Arm
L1	4	2
M1	2	2
L2	1	0
M2	0	1
L3	0	0
M3	2	0
L4	0	1
Total digital	9	6
M1 + L2	2	6
M2 + L3	3	3
M3 + L4	0	6
Total interspace	5	15
Other	0	18

FIG. 3. Projection of sensation in relation to the innervation territories of the palmar digital nerves (PDNs). L1 = lateral PDN of the thumb; M1 = medial PDN of the thumb; L2 = lateral PDN of the index: M2 = medial PDN of the index; L3 = lateral PDN of the middle finger; M3 = medial PDN of the middle finger; L4 = lateral PDN of the ring finger Figures in the Table refer to number of experiments, when stimulating either at the wrist or in the upper arm, during which evoked sensations were projected to the territory of one PDN, adjacent PDNs to neighbouring fingers (i.e. a digital interspace), or elsewhere. Only experiments involving skin nerve fascicles are listed.

wrist (fig. 4). The area contained between such a line, the main cutaneous wrist crease and the contours of the palm measured between 116.5 cm^2 and 131.9 cm^2 for the different subjects, although it must be pointed out that these are not *total* areas of median supplied glabrous skin but, like the MPTs themselves, projections of such areas onto a flat surface. The mean MPT when stimulating at the wrist was thus

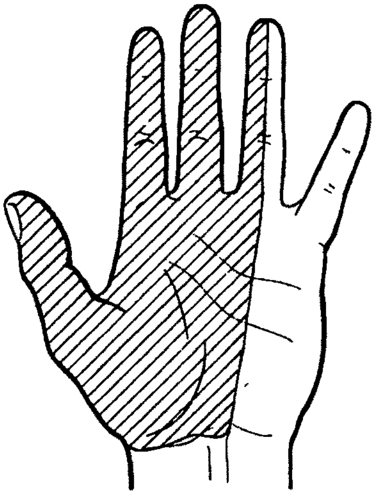


FIG. 4. Pooled maximal projection territories mapped in the course of 35 experiments in one subject. The hatched area corresponds to the median nerve territory as outlined by this method.

found to be 10 ± 3 per cent (mean ± SD) of the area of glabrous skin supplied by the median nerve.

Stimulation in the upper arm. Again, projected fields of elementary sensations evoked by INMS in skin nerve fascicles in the upper arm were not randomly scattered in the hand. Sixty-seven per cent of them were contained within a circumscribed area corresponding to a particular digital interspace (figs. 5A, B). At saturation the MPT coincided with the innervation territory of one single or two adjacent palmar digital nerves in 21 out of 39 experiments. Furthermore, the digital

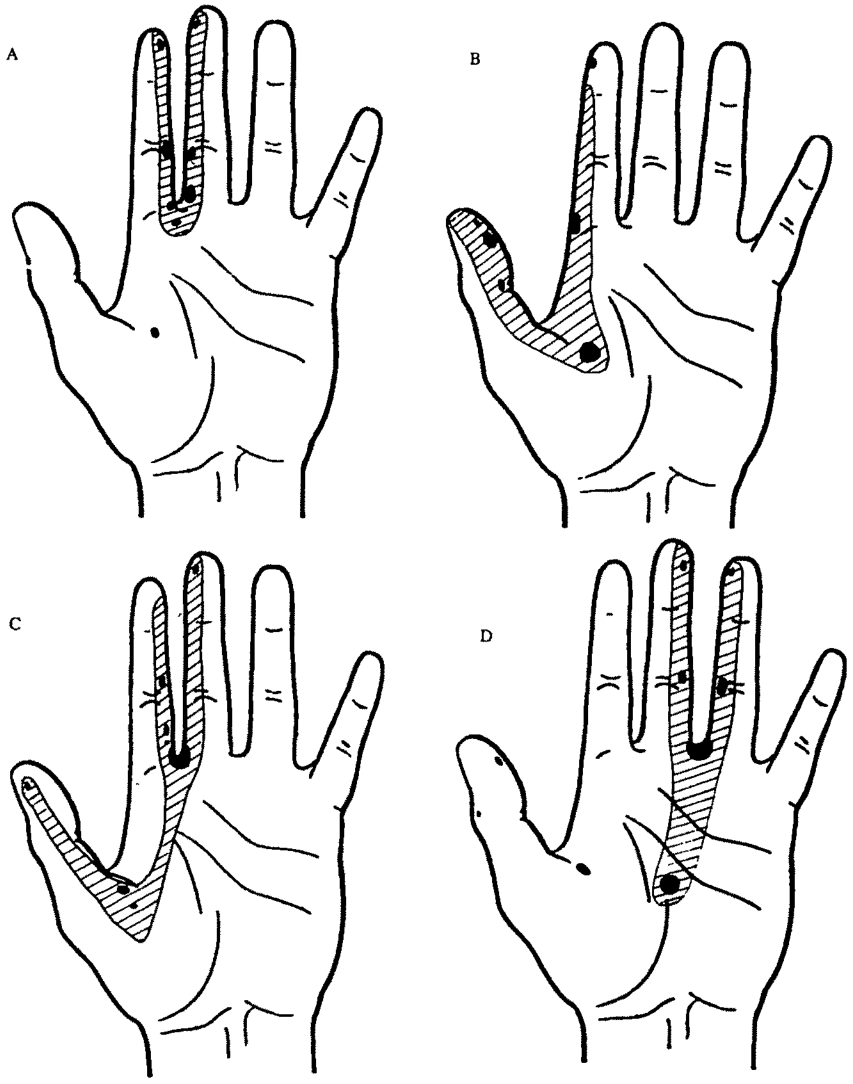


FIG. 5. Projections of elementary sensations (filled-in areas) and maximal projection territories (hatched areas) mapped during 4 representative experiments when stimulating in the upper arm. Evoked sensations were typically projected to a digital interspace plus a wedge of palm, although sometimes additional areas were involved.

nerves involved supplied separate fingers and therefore a digital interspace rather than both halves of a finger (fig. 3). In 6 other experiments the MPT also corresponded to an interspace except for one or two discordant sensations projected elsewhere. In the remainder, projection was to the territories of 2 nonadjacent digital nerves in 1 case, 3 digital nerves in 9 cases and 4 digital nerves in 2 cases. Occasionally the MPT extended beyond the midline at the pulp of a finger (fig. 5B). This was also sometimes seen when stimulating at the wrist (fig. 2C). More rarely the reverse occurred, so that the tip of a finger was spared. Projection exclusively to the palm of the hand was never encountered, but MPTs commonly extended to involve a wedge of the skin of the palm (figs. 5B–D).

The MPT never covered the whole of the median nerve territory. Its mean area when stimulating in the upper arm was 23.7 cm^2 or, expressed as a percentage, 16 ± 6 per cent of the area of glabrous skin supplied by the median nerve. This is significantly greater than the corresponding value obtained when stimulating at the wrist ($P < 0.01$).

DISCUSSION

Spinal root axons need to reassemble into the groupings of afferent and efferent fibres present in terminal nerve branches. This sorting out may take place, partly or wholly, in the brachial and lumbosacral plexuses. It is, for instance, known that most proximal fascicles in dog sciatic nerve contain sensory fibres from each of its segmental sources (Ueyama, 1978), indicating considerable regrouping of fibres in the lumbosacral plexus. More distally, interfascicular communications may also subserve this function, although their complexity has led Seddon to conclude that 'this intermingling . . . is rather overdone, and . . . much of it is fortuitous' (1975). Intraneural stimulation in alert human subjects provides a new means of studying the contents of nerve fascicles in terms of the relative proportions of motor units and cutaneous afferents, and of their peripheral projections. The results obtained with this method suggest that, at least for the median nerve, most of the nerve fibre transpositions required to regroup spinal root fibres into the constituents of terminal nerve branches occur at the level of the brachial plexus, while fascicular plexuses within the nerve trunk may represent a safety mechanism to safeguard against the effects of partial nerve injuries.

Legitimacy of the Indirect Tracing Method Used

The maximal projection territories of the compound sensations evoked at stimulus amplitudes between 1 and 4 V are in our view the result of activating the complement of cutaneous sensory fibres contained in a fascicle. It might be argued that only a fraction of the fibres within a fascicle—a 'microbundle'—is activated at the stimulus amplitudes used. This is unlikely on anatomical grounds alone, since there is no evidence of compartmentalization of fascicular contents except at points of fusion or division of fascicles. Furthermore, small electrode displacements did not usually alter the size of the maximal projection territory. On one particular occasion all sensation could be abolished by advancing or retracting the electrode, but it reappeared with identical MPT when the electrode tip was returned to its original position. Lastly, in a majority of experiments it was clear that beyond a certain stimulus amplitude there was no further growth in MPT. Such saturation is very much in favour of activation of whole fascicles rather than microbundles.

Another possibility is that spillover of current to adjacent fascicles occurred, so that more than one fascicle would be represented in the maps drawn by our subjects. While this may have happened on isolated occasions it is unlikely to have been substantial. Several studies have shown that the perineurium is a structure of high resistance which will tend to keep action currents within the fascicle (Rashbass and Rushton, 1949; Clark and Plonsey, 1968). Hagbarth *et al.* (1970) also observed that 'overhearing' between neighbouring fascicles during intraneural recording was negligible.

The double electrode experiments reported above, although performed on nerves other than the median, provide the strongest evidence that the stimulus amplitudes used are sufficient to activate all fibres within one fascicle, and one fascicle only. The results of the first three indicate that recordable stimulus spread beyond the fascicle containing the electrode tip did not occur. The fourth showed that saturation of the myelinated fibre components of the compound action potential induced by INMS occurred at currents far below the ceiling used in our median nerve experiments. Saturation of the unmyelinated fibre components occurred much later, although still within the range of currents used. Nevertheless, the MPTs mapped in our experiments may not have accurately reflected the projection territories of all unmyelinated fibres contained within a fascicle, since pain perception may have been depressed by changes in excitability of C fibres during 5 Hz stimulation, and by central effects dependent on massive large fibre activation (Torebjörk, 1981). Patterns of cutaneous sensory loss following nerve lesions suggest that the fascicular territories of unmyelinated fibres may be larger than those of myelinated fibres (Rivers and Head, 1908).

Suppressive interactions at central level between simultaneously delivered nonpainful inputs must also be considered. It is known that sensations in one finger may mask those arising from neighbouring regions of the hand (Ferrington *et al.*, 1977; Gandevia *et al.*, 1983). In view of the intensity of the sensations evoked at high stimulus amplitudes in our experiments, some outlying weaker sensations may have been missed by the subjects. MPTs would then be somewhat smaller than true fascicular projection territories, although this effect is likely to have been minimal in view of the good correspondence between MPTs when stimulating at wrist level and digital nerve innervation territories (fig. 2), and between the traditionally accepted median nerve territory and that oulined by our method (fig. 4). It is also possible that central inhibitory effects might suppress sensations arising from the activation of a small number of deeply seated motor units in a predominately cutaneous fascicle. The resulting contraction might be neither visible nor palpable.

Nevertheless, activation of a substantial number of motor units should not go unnoticed.

On the strength of these arguments it can be stated that (1) the intraneural stimulation and recording profiles obtained in our experiments largely reflect the composition of nerve fascicles and (2), the MPTs represent the projection areas of the low threshold mechanoreceptive afferents contained in a fascicle.

Segregation of Muscle and Skin Nerve Fascicles

The opinions in the literature regarding this question are conflicting. Some early authors (Stoffel, 1913; Dejerine *et al.*, 1915; Langley and Hashimoto, 1917) felt that muscle and cutaneous nerve branches retain their identity in the proximal segments of the nerve. Others argued that extensive redistribution of fibres takes place along the length of the nerve, with mingling of cutaneous afferents and motor units (McKinley, 1921). Sunderland argued against rigid intraneural localization of terminal branch fibre bundles, based on his finding of a complex fascicular plexus in human peripheral nerves (Sunderland, 1945; Sunderland *et al.*, 1959; Sunderland, 1978). Such fascicular intercommunications, repeatedly confirmed in subsequent studies (Tamura, 1969; Jabaley *et al.*, 1980), would allow proximal dispersal of branch fibres, which in turn would explain the clinical observation that incomplete proximal nerve lesions often produce surprisingly little detectable loss of function (Sherren, 1908; Babcock, 1928; Seddon, 1942). However, there are alternative explanations for this phenomenon, as will be discussed later.

Our results suggest that despite the changing anatomical fascicular pattern, a degree of segregation of muscle and skin nerve fibres is present in the proximal segments of the median nerve. At the wrist there was obviously a large proportion of seemingly pure skin fascicles, which would have been even greater if fascicles to the middle and ring fingers had been more accessible. At upper arm level 20 to 40 per cent of fascicles appeared to project exclusively to the skin. If they contained any motor units, their numbers must have been small enough not to cause visible contraction. Even overtly mixed fascicles could easily be identified as either predominantly cutaneous or predominantly motor. By comparison the number of 'pure' muscle nerve fascicles was small, although it should be pointed out that almost half of the mixed nerve fascicles supplying mainly muscle (Group 4), contained only one or two cutaneous fibres that were felt during INMS. The associations of fibres observed in mixed fascicles are in keeping with Sunderland's (1945) histological observations, for example, the mingling at wrist level of fibres to the thenar eminence with cutaneous fibres from the radial aspect of the thumb. At more proximal levels in the nerve, Sunderland's approach would not have detected the selective origin of the cutaneous fibres contained in a mixed fascicle.

A degree of fascicular segregation has long been known to microneurographists, who identify skin and muscle nerve fascicles by the presence of motor unit activity, the peripheral source of afferent units and by the differential character of any sympathetic efferent activity encountered (Delius *et al.*, 1972; Hagbarth *et al.*, 1972).

There is anecdotal clinical and morphological evidence pointing in the same direction. For example, Rennels and Ochoa (1980) reported a case of brachial plexus neuropathy with selective damage to the fibres destined to become the anterior interosseus nerve, suggesting bundling of fibres far from the point where they emerge as peripheral branches. It has also been noted that mixed nerve biopsy in a pure motor neuropathy may show selective involvement of some fascicles while sparing others (Ochoa, 1980).

Cutaneous Territories of Skin Nerve Fascicles

Hagbarth *et al.* (1970) mapped the receptive fields of median nerve fascicles in awake human subjects by means of gentle stroking of the skin during microneurography. In agreement with our observations, they found fascicular fields to be considerably smaller when recording at the wrist than in the upper arm. However, territories of upper arm fascicles often appeared to cover three of four fingers and much of the palm. A possible source of error in these outsize maps could be the extreme sensitivity of pacinian corpuscle units, which may respond to gentle taps applied many centimetres outside their receptive endings. The number of pacinian corpuscle units is naturally greater in the larger fascicles at elbow level.

From our results it is apparent that median nerve fascicles, both at the wrist and in the arm, supply a circumscribed and relatively well-defined area of skin. At wrist level, fascicles contain fibres from one or, less commonly, two adjacent palmar digital nerves. In the upper arm fascicles usually supply adjacent halves of neighbouring fingers, that is, one digital interspace, although a deviation from this pattern is more common than at the wrist. Sometimes three or rarely four digital nerves are represented in a proximal fascicle. Clearly, there must be considerable variation between subjects, between different nerves and between various levels in the same nerve. Proximal median nerve fascicles in the subjects studied, however, never contained a random assortment of fibres from all of the nerve's distal branches. Even though a few cutaneous fibres may travel in muscle nerve fascicles and *vice versa*, and although some sensory fibres in skin nerve fascicles may project outside the orderly territories described above, our results do not support the idea that fibres from all peripheral sources intermingle completely along the course of a nerve. Some dispersal occurs, but the overall result of interfascicular communications—at least as far as cutaneous fibres are concerned—appears to be selective merging of fascicular contents in an orderly and predictable fashion. This organization may be lost as a result of nerve injury and regeneration, following which fascicular territories are broken up into several discontiguous zones (Hallin *et al.*, 1979).

It remains to be explained why, if muscle nerve fibres and cutaneous afferents are relatively segregated and the latter project to a circumscribed area of skin, partial proximal nerve lesions often do not produce a focal sensory or motor deficit comparable to that seen following distal nerve lesions. This apparent preservation of function can readily be explained if there is overlap between the territories of proximal nerve fascicles. Such an overlap has been shown in the greater auricular nerve of the rabbit (Terzis, 1981). Since there are about ten fascicles in the median nerve at the level in the upper arm used in our experiments (Sunderland and Bradley, 1949) and only three digital interspaces plus the radial aspect of the thumb, it follows that each area of skin—at least in the fingers—should on average be represented in two fascicles, allowing for the existence of two pure muscle nerve fascicles at this level. Much more extensive redistribution of fibres must take place further proximally in the nerve trunk and at brachial plexus level to account for the generally accepted overlap of 3 to 5 dermatomes at any one point of skin (Denny-Brown *et al.*, 1973; Dykes and Terzis, 1981). In view of the fact that proximal nerve fascicular territories in no way resemble dermatomes, it can be concluded that interfascicular communications in the distal segments of peripheral nerves do not primarily serve the function of translating groupings of spinal root axons into innervation patterns at terminal branch level. They may, however, have developed as an extension of the safety mechanism inherent in dermatomal overlap: double representation of target tissue in the proximal portion of a peripheral nerve is undoubtedly more advantageous in cases of partial nerve injury than a simple cable structure.

Practical Relevance in Nerve Injury and Repair

Repair of nerve lesions with axonal interruption ideally contemplates successful reconnection of regenerated axons to their private original targets. While in crush lesions the basement membrane surrounding each nerve fibre may be preserved to guide growing axons to their original targets (Young, 1942; Thomas, 1964), in cut lesions functional recovery is less successful due to mismatch and recurrent growth. In most instances following nerve division, fascicular repair produces better results than epineural repair (Bora, 1967; Grabb *et al.*, 1970). At distal levels the advantage of apposing corresponding fascicular ends is obvious, since there is little if any functional overlap between fascicles. However, following injury to the proximal segments of a nerve, little would be gained by employing the much more laborious techniques of fascicular or group funicular suture, unless peripheral branch fibres remained to some extent localized within the nerve trunk. Our results suggest that proximal nerve fascicles do retain a measure of identity in terms of their predominant commitment to either muscle or a circumscribed area of skin, thus endorsing the need for accurate matching of fascicular ends at all levels whenever possible.

ACKNOWLEDGEMENTS

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CEREBRAL GLUCOSE UTILIZATION, AS MEASURED WITH POSITRON EMISSION TOMOGRAPHY IN 21 RESTING HEALTHY MEN BETWEEN THE AGES OF 21 AND 83 YEARS

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SUMMARY

Positron emission tomography (PET) scanning with ^{18}F-2-deoxy-D-glucose was employed to examine hemispheric and regional rates of cerebral glucose utilization in 21 resting healthy men between the ages of 21 and 83 years. The eyes of the subjects were covered and the external auditory canals were plugged with cotton in the 45 minutes following injection of tracer. Mean hemispheric cerebral metabolic rates for glucose (CMR_{glc}) averaged 4.3 to 4.4 mg. 100 $g^{-1}.min^{-1}$, and mean hemispheric grey matter glucose utilization, $(CMR_{glc})_{grey}$, averaged 5.2 to 5.3 mg.100 $g^{-1}.min^{-1}$. Neither parameter was correlated significantly with age, nor were their right/left ratios correlated with age ($P > 0.05$). The mean ratios, furthermore, did not differ significantly from 1. Regional cerebral metabolic rates for glucose, $rCMR_{glc}$, at each of 31 identified midline and bilateral structures also were not correlated significantly with age. Mean $rCMR_{glc}$ ranged from 2.6 mg.100 $g^{-1}.min^{-1}$ at the centrum semiovale to 6.2 mg. 100 $g^{-1}.min^{-1}$ at the precentral gyrus of the frontal lobe and precuneus of the parietal lobe. The results indicate that the cerebral metabolic rate for glucose is not correlated with age in healthy men.

INTRODUCTION

Since the report by Fazekas *et al.* (1952), the relation between age and brain oxidative metabolism in man has been examined repeatedly, yet the issue remains unresolved. Some reports indicate that the cerebral metabolic rate for oxygen (CMR_{O_2}) is not reduced in the elderly (Shenkin *et al.*, 1953; Scheinberg *et al.*, 1953; Dastur *et al.*, 1963), whereas other reports suggest a reduction (Fazekas *et al.*, 1952;

Lassen *et al.*, 1960; Gottstein and Held, 1979; Frackowiak *et al.*, 1980). Glucose is the major substrate for brain oxidative metabolism (Sokoloff, 1976), and the cerebral metabolic rate for glucose (CMR_{glc}) is reported to be lower in healthy elderly than in young subjects (Dastur *et al.*, 1963; Gottstein and Held, 1979; Kuhl *et al.*, 1982). Cerebral blood flow (CBF), which usually is coupled to brain oxidative metabolism (Kety, 1956; Raichle *et al.*, 1976; Sokoloff, 1976), is reported by some investigators to be independent of age (Shenkin *et al.*, 1953; Lassen *et al.*, 1960; Dastur *et al.*, 1963), and by others to be reduced in the elderly (Fazekas *et al.*, 1952; Scheinberg *et al.*, 1953; Obrist, 1978; Gottstein and Held, 1979; Naritomi *et al.*, 1979; Melamed *et al.*, 1980; Dickinson *et al.*, 1980; Frackowiak *et al.*, 1980).

Recently, positron emission tomography (PET), with ^{18}F-2-deoxy-D-glucose (^{18}FDG) as a positron-emitting glucose analogue, has made it possible to determine not only CMR_{glc}, but also regional cerebral metabolic rates for glucose, $rCMR_{glc}$ (Sokoloff *et al.*, 1977; Phelps *et al.*, 1979; Huang *et al.*, 1980). As compared with the regional analysis of CBF with the ^{133}Xe clearance technique (Lassen *et al.*, 1978), PET has the advantage of providing information about subcortical as well as cortical structures. We therefore decided to use PET to re-examine the relation between age and overall, as well as regional, cerebral glucose metabolism in healthy men. An abstract of this work has been published (Duara *et al.*, 1982).

METHODS

Selection of Subjects

A medical questionnaire was mailed to all prospective subjects, who were invited for screening if the questionnaire indicated (1) the absence of a continuing medical disorder having an impact on daily physical or intellectual activities and (2), the absence in the past or present of a disorder that involved, or was likely to involve, the central nervous or cardiovascular systems. For example, individuals with mild degenerative joint disease were accepted, but those with rheumatoid arthritis were rejected because of the known associated vascular and neurological complications.

Screening included a review of the medical history, a thorough physical examination and the following laboratory studies: (1) complete blood count, serum electrolytes, creatinine, cholesterol, triglycerides and blood urea nitrogen to screen for haematological, metabolic and renal disease; (2) serum protein, albumin/globulin ratio, bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase to screen for liver disease; (3) fasting blood glucose, serum T_3, T_4 and TSH to screen for diabetes and thyroid disease; (4) VDRL reaction and antinuclear antibodies to screen for syphilis and immunological disease; (5) serum folic acid and vitamin B_{12} to identify deficiencies of these vitamins; (6) a resting electrocardiogram to screen for ischaemic heart disease and cardiac arrhythmias; (7) pulmonary function tests (vital capacity, forced expiratory volume, maximum minute ventilation); and (8) radiography of the chest (posterior-anterior and lateral views) and neck to identify cardiac, large vessel or pulmonary pathology.

Subjects were accepted for PET if (1) the above tests revealed no abnormalities; (2) there was no evidence of previous myocardial infarction, angina pectoris, arrhythmias, rheumatic or other heart disease or peripheral vascular disease, and supine blood pressure in both arms was less than 170 mm Hg systolic and 95 mm Hg diastolic; (3) there was no evidence or history of stroke, transient cerebral ischaemia, seizures, recurrent headache, significant head trauma with sustained anterograde or retrograde amnesia or impairment of consciousness (isolated findings of diminished or absent ankle jerks or of vibration sensation in the feet of subjects over 65 years of age, or of a mild senile tremor, were acceptable); (4) corrected visual acuity was at least 20/70 with full visual fields in each eye; and (5) there was no indication of alcohol or drug abuse or of a major psychiatric disorder. The subjects also were administered the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1958).

Consent procedure. Screened subjects were asked to sign an informed consent which described the purpose of the study, the tests to be performed and the risks involved, including radiation exposure. Total radiation exposure was kept below limits established for normal volunteers in medical research (*see* Acknowledgements).

PET Scanning

Preparation of subjects. Subjects were familiarized with the PET procedure prior to the scheduled scan. They were asked to avoid coffee, tea, cigarettes, alcohol or medications (including antihistamines and aspirin) for 24 h before the scan. A subject reported about 5 h before a scan, ate breakfast, but did not eat thereafter so as to minimize hyperglycaemia during scanning (Phelps *et al.*, 1979). Indwelling 20 gauge catheters (Angiocath, Deseret Co., Sandy, UT) were placed in dorsal veins of both hands and in an antecubital vein; 0.45 per cent (w/v) saline was infused through the catheters to keep the veins patent. Both hands were heated in specially constructed boxes (McGuire *et al.*, 1976; Margolin, Duara and Rapoport, unpublished observations), so as to arterialize venous blood (Phelps *et al.*, 1979). Thermoprobes on the dorsa of both hands were connected to telethermometers (No. 73A, Yellow Springs Instrument Co., Yellow Springs, OH) that could activate heating elements in the boxes to maintain skin temperature at 42 to 44° C. The radial artery was punctured at least 1 h before PET scanning to obtain blood for determination of pH, Pa_{O_2} and Pa_{CO_2}.

Standardization of PET scan. ^{18}FDG was prepared by the method of Fowler *et al.* (1981). Its radiochemical purity, which equalled or exceeded 95 per cent, was determined with high pressure liquid chromatography when using a carbohydrate analysis column (No. 84038, Waters Associates, Milford, MA) through which $CH_3CN:H_2O$ (95:5, v/v) flowed at a rate of 2 ml . min^{-1}. Apyrogenicity of each sample was ascertained with a Limulus Amebocyte Lysate test (M.A. Bioproducts, Walkersville, MD), and occasionally with the USP Rabbit Pyrogen Test (Bureau of Biologics, Food and Drug Administration, Bethesda, MD). Sterility was assured by passing injectate through a filter with 0.22 μm-diameter pores (Millipore Corp., Bedford, MA), and by using autoclaved glassware.

A 2500 ml plastic cylinder, known as a 'phantom', was filled with a uniform concentration of $18F^-$ and was scanned with the ECAT II Positron Tomograph (ORTEC, Life Sciences, Oak Ridge, TN) in the medium resolution mode. Images were reconstructed to obtain image densities in ECAT units. Radioactivity of plasma samples was determined with a gamma counter (Model 8000, Beckman Instruments, Irvine, CA), which was set at a window opening of 20 to 2000 keV. Cpm were compared to cpm of a ^{85}Sr standard to estimate counting efficiency (Brinkman *et al.*, 1963). A factor for converting ECAT units to μCi . g^{-1} was calculated from the relation between phantom ECAT values and decay-corrected radioactivity.

PET scanning of subjects. Fifteen to 30 min prior to the injection of ^{18}FDG, the subject lay down on the bed of the ECAT II Positron Tomograph in a darkened room. His eyes were covered with a mask and industrial cotton (Bilsom Propp-o-Plast, No. 5022, Billesholm, Stockholm) was inserted in the external auditory canals to reduce extraneous auditory input. (Audiometry tests under such conditions indicated that broad-band speech amplitude was reduced by 4 dB, amplitudes at frequencies below 100 Hz were reduced by 4 to 6 dB, at frequencies between 1000 and 2000 Hz by 14 to 16 dB, and at frequencies of 3000 to 8000 Hz by 20 to 24 dB.)

Three to 5 mCi of ^{18}FDG in 10 ml of 0.9 per cent (w/v) NaCl were injected into an antecubital vein during 30 s, following which 1 ml samples of arterialized venous blood were removed at timed intervals from a vein of a heated hand. Plasma aliquots were taken for measurement of glucose concentration (Glucose Analyzer II, Beckman) and of ^{18}F radioactivity, which was counted under the same conditions as were the phantom samples. Radioactivities were decay-corrected to injection time.

^{18}FDG is lost mainly by renal excretion, and the bladder is a major organ at risk for radiation (Phelps *et al.*, 1979). We minimized this risk by having the subject urinate 45 min after ^{18}FDG was injected, and following PET scanning. Urine production was maximized by infusing 0.45 per cent (w/v) NaCl through the intravenous catheters, 500 ml before injection of ^{18}FDG, 500 ml in the first hour after injection and 250 ml in the subsequent 90 min. At 45 min, furthermore, the mask covering the eyes and the cotton in the auditory canals were removed in the darkened and quiet ECAT room.

Between 45 and 140 min after ^{18}FDG was injected, up to 7 serial PET slices were obtained with the ECAT II in the medium resolution mode (full width at half-max = 1.7 cm in image and axial planes). PET slices had at least 7.5×10^5 coincidence counts, were 1.7 cm thick and were separated from each other by 1.4 cm. Slices were taken parallel to and between 5 and 100 mm above the line connecting the inferior orbital rim to the external auditory meatus, called the inferior orbitomeatal (IOM) line. Images later were reconstructed and attenuated with the ORTEC attenuation correction program, using a uniform attenuation coefficient ($\mu = 0.088$) and an operator-drawn ellipse to define the edge of the scalp.

Regions of interest. Because size and shape of heads varied among individuals, PET scans at identical levels above an externally defined IOM line did not always include corresponding brain regions. In order to evaluate corresponding regions among brains of different subjects, we compared each scan with anatomical sections of a single human brain at specified levels above the IOM line for that brain (Eycleshymer and Schoemaker, 1911), and defined the 'intrinsic' height for each scan from the comparable brain section. Regions of interest, as noted in fig. 1, then were identified by comparing the scan with the section, and were outlined with the computer program of the ECAT II to provide mean and maximum ECAT values and pixel numbers, where area/pixel = 0.083 cm^2. ECAT values were converted to brain radioactivity with the conversion factor obtained by scanning the phantom (*see above*).

rCMR$_{glc}$ was calculated in units of mg.100 g^{-1}.min^{-1} with an operational equation which incorporates the rate of accumulation of ^{18}FDG by brain (Huang *et al.*, 1980). The lumped constant in this equation, a measure of the predilection of the brain for ^{18}FDG as compared to glucose, was taken as 0.418 (Huang *et al.*, 1980). The four transfer constants for grey matter regions were taken, in units of min^{-1}, as $k_1^* = 0.102$, $k_2^* = 0.130$, $k_3^* = 0.062$ and $k_4^* = 0.0068$. For white matter regions, they equalled $k_1^* = 0.054$, $k_2^* = 0.109$, $k_3^* = 0.045$ and $k_4^* = 0.0058$ (Huang *et al.*, 1980). The operational equation was solved with the appropriate transfer constants, values for brain radioactivity (μCi.g^{-1}) at the time of scanning, plasma radioactivity (dpm.ml^{-1}) to this time and the average plasma glucose concentration (mg.100 ml^{-1}).

Weighted means of cerebral glucose utilization. Because an identified brain region often appeared in more than one PET slice of an individual brain (*see* fig. 1), we calculated as follows the weighted mean rCMR$_{glc}$ for a region from the number of slices in which the region was identified and from the regional surface area per slice. Let $(\mathrm{rCMR}_{glc})_i$ equal the glucose metabolic rate for the region in slice i, and let N_i equal the surface area of the region of interest in slice i. Then, the weighted mean metabolic rate for the region equals,

$$\mathrm{rCMR}_{glc} = \frac{\Sigma_i (\mathrm{rCMR}_{glc})_i \, N_i}{\Sigma_i \, N_i} \qquad \text{(Equation 1)}$$

where i = 1, 2 . . . are individual slices.

If the region of interest is an entire hemisphere (including grey matter, white matter and ventricles), then rCMR$_{glc}$ equals the net hemispheric metabolic rate for glucose, CMR$_{glc}$, and is also given by Equation 1, where i = 1, 2 . . . 5 are individual slices between 30 and 80 mm above the IOM line (fig. 1) (these limits were chosen because they applied uniformly to most brains), N_i is the entire hemispheric surface area in slice i, and $(\mathrm{rCMR}_{glc})_i$ is the cerebral metabolic rate for glucose in the entire hemisphere at slice i. CMR$_{glc}$ could be calculated with transfer constants of grey or of white matter (*see* Results).

Finally, the weighted mean metabolic rate for glucose in grey matter of an entire hemisphere, defined

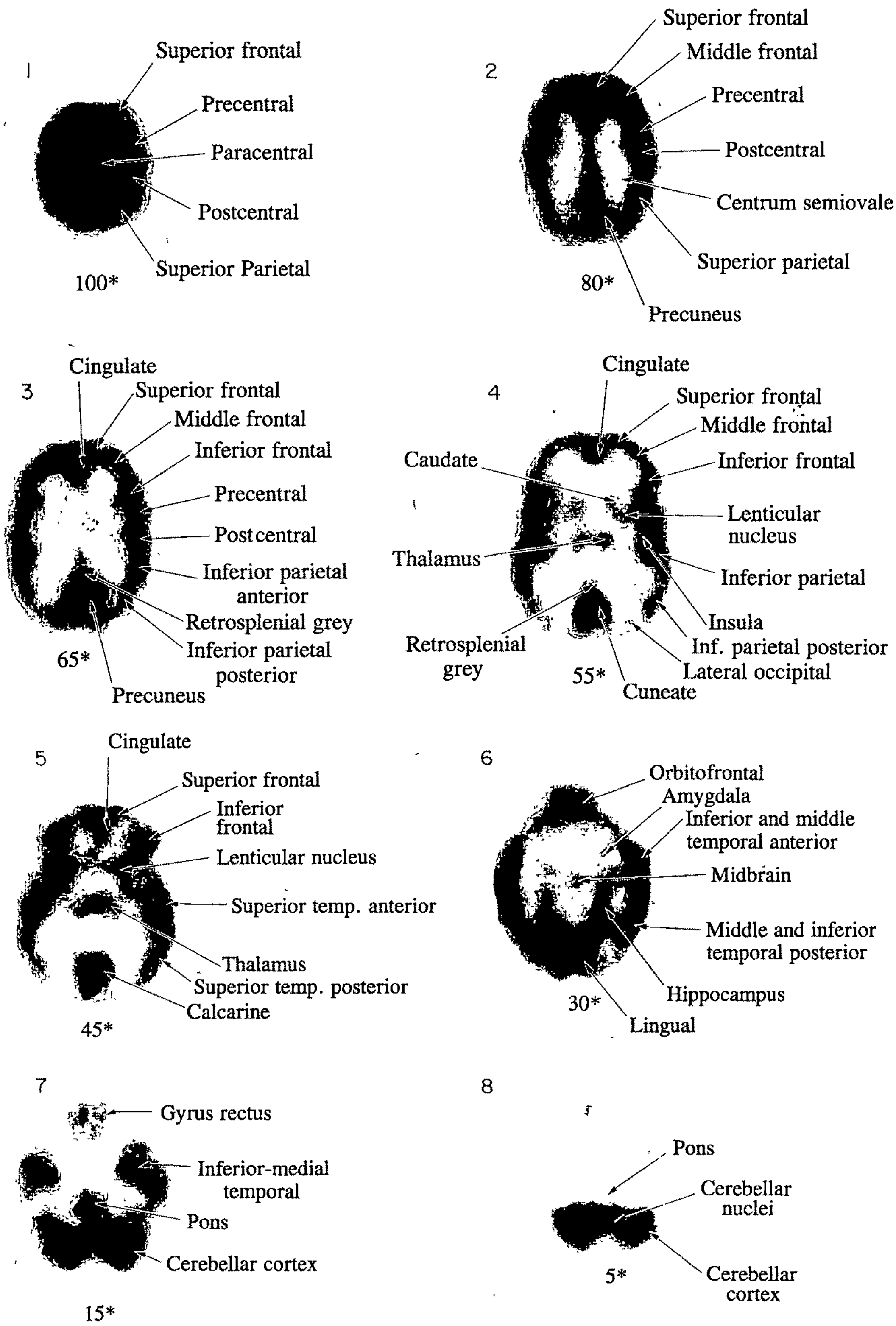

FIG. 1. PET scans and regions of interest at different levels (mm) above the inferior orbitomeatal (IOM) line The levels are defined in relation to the atlas of Eycleshymer and Schoemaker (1911)

as $(\mathrm{CMR}_{\mathrm{glc}})_{\mathrm{grey}}$, was calculated as follows, where $(\mathrm{rCMR}_{\mathrm{glc}})_{\mathrm{grey},\,\mathrm{i}}$ equals the cerebral metabolic rate for glucose in all grey matter regions of slice i, and N_i equals the net area of grey matter in this slice,

$$(\mathrm{CMR}_{\mathrm{glc}})_{\mathrm{grey}} = \frac{\Sigma_\mathrm{i}(\mathrm{rCMR}_{\mathrm{glc}})_{\mathrm{grey,i}}\,\mathrm{N}_\mathrm{i}}{\Sigma_\mathrm{i}\,\mathrm{N}_\mathrm{i}} \quad \text{for i} = 1, 2 \ldots \qquad \text{(Equation 2)}$$

Statistics. Significance of differences between means was examined by Student's t test, and parameters were correlated with age by Pearson correlation analysis (Dixon and Massey, 1957). The criterion for significance was $P \leqslant 0.05$.

RESULTS

Twenty-one male volunteers, between the ages of 21 and 83 years, were selected for positron emission tomography (PET) scanning. The subjects had completed a high school education and 18 had obtained at least a Bachelor's degree. Nineteen were right-handed and 2 were left-handed (aged 33 and 51 years).

Mean values for physiological and psychological parameters which characterize the sample are listed in Table 1, as well as coefficients of correlation (r) with age. Systolic and diastolic blood pressures were not correlated significantly with age, probably because hypertensive subjects were excluded from the study. Both $\mathrm{Pa}_{\mathrm{CO}_2}$ and $\mathrm{Pa}_{\mathrm{O}_2}$ were correlated significantly and negatively with age, whereas arterial pH was correlated significantly and positively. The performance scale score of the Wechsler Adult Intelligence Score (WAIS), which like the verbal scale score is

TABLE 1. CHARACTERISTICS OF SUBJECTS

Measurement	*Units*	*Mean ± SE*	*Correlation with age (r)*
No. of subjects		21	—
Age	years	50.8 ± 4.0	—
Weight	kg	80 ± 2	n.s.
Heart rate	beats. min^{-1}	76 ± 2	n.s.
Systolic blood pressure	mm Hg	133 ± 3	n.s.
Diastolic blood pressure	mm Hg	80 ± 1	n.s.
$\mathrm{Pa}_{\mathrm{O}_2}$	mm Hg	83 ± 2	−0.47*
$\mathrm{Pa}_{\mathrm{CO}_2}$	mm Hg	37 ± 1	−0.53*
Arterial pH	pH units	7.40 ± 0.01	0.53*
Fasting venous plasma glucose	mg . 100 ml^{-1}	87 ± 3	n.s.
WAIS IQ (age corrected)			
Performance		118 ± 3	
Verbal		127 ± 3	
Full		124 ± 3	
WAIS—scaled			
Performance		54 ± 3	−0.62*
Verbal		83 ± 3	n.s.
Full		137 ± 5	n.s.

* Statistically significant correlation with age ($P < 0.05$).

TABLE 2 WEIGHTED MEANS FOR THE CEREBRAL METABOLIC RATE FOR GLUCOSE OF RIGHT AND LEFT HEMISPHERES, AND FOR GREY MATTER IN RIGHT AND LEFT HEMISPHERES

Parameter	*Right hemisphere*	*Correlation with age (r)*	*Left hemisphere*	*Correlation with age (r)*	*Right/left*	*Correlation with age (r)*
	$mg.100\,g^{-1}\ min^{-1}$		$mg\ 100\,g^{-1}.min^{-1}$			
CMR_{glc}	4.3±1.1*	−0.22	4.4±1.1	−0.21	0.99±0.05	0.1
$(CMR_{glc})_{grey}$	5.2±1.2	−0.21	5.3±1.2	−0.20	0.98±0.04	−0.01

*Mean ± SD (n = 21). No correlation coefficient was statistically significant ($P > 0.05$). CMR_{glc} was calculated by Equation 1 and $(CMR_{glc})_{grey}$ by Equation 2, with the use of grey matter transfer constants

age-uncorrected (Wechsler, 1958), was correlated significantly and negatively with age.

The calculated value of the weighted mean hemispheric CMR_{glc} was quite independent of whether white matter or grey matter constants were inserted into the operational equation (Phelps *et al.*, 1979) and Equation 1. Mean hemispheric CMR_{glc} in 5 subjects, when calculated with white matter constants, exceeded the mean value when calculated with grey matter constants by less than 8 per cent. We therefore used only one set of constants, those for grey matter, to obtain CMR_{glc} for the entire 21 subjects. Table 2 presents these values as well as means for hemispheric grey matter glucose utilization, $(CMR_{glc})_{grey}$, as calculated with Equation 2.

Neither CMR_{glc} nor $(CMR_{glc})_{grey}$ at either hemisphere was correlated significantly with age. The lack of a significant relation with age is further illustrated in fig. 2 for $(CMR_{glc})_{grey}$. In addition, the right/left ratios for CMR_{glc} and for

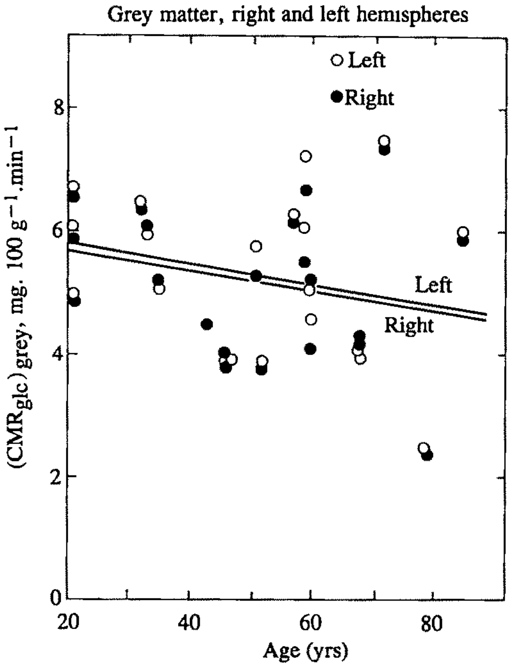

FIG. 2. Relation of the cerebral metabolic rate for glucose in grey matter of the hemispheres to age, for 21 subjects. The least-squares fits to the data are given in the figure; their slopes do not differ significantly from 0 ($P > 0.05$).

$(CMR_{glc})_{grey}$ were not correlated significantly with age, and the mean right/left ratios did not differ significantly from 1. Higher mean values for $(CMR_{glc})_{grey}$ than for CMR_{glc} reflect the inclusion of white matter and ventricular areas in regions of interest when calculating CMR_{glc}. An average of 4.4±3.5 (SD) slices between 30 and 80 mm above the IOM line were analysed per brain when calculating CMR_{glc} and $(CMR_{glc})_{grey}$. The mean net surface area of the hemispheric regions of interest in these slices equalled 277 cm^2 for the left hemisphere and 267 cm^2 for the right.

Table 3 presents weighted means for $rCMR_{glc}$, as calculated with Equation 1, at 31 identified bilateral and midline regions (*see* fig. 1). Occasionally, less than 21 brains were analysed because some PET slices were unavailable. The table also presents the mean number of slices examined per brain for a given region, and the net surface area examined in these slices (given for right-sided or midline regions).

TABLE 3 WEIGHTED REGIONAL CEREBRAL METABOLIC RATES IN RELATION TO AGE AT BILATERALLY SYMMETRICAL AND MIDLINE BRAIN REGIONS

					Right side		*Left side*	
Brain region	*mm above IOM line*	*No of subjects*	*Net surface area (cm^2)*	*No of slices*	*$rCMR_{glc}$ ($mg\ 100\ g^{-1}\ min^{-1}$)*	*Correlation with age (r)*	*$rCMR_{glc}$ ($mg.100\ g^{-1}\ min^{-1}$)*	*Correlation with age (r)*
Frontal lobe								
Superior frontal gyrus	80-100	18	4.9±3.2*	1.4±0.5	5.81±1.59	−0.27	5.73±1.54	−0.28
	60-80	20	3.2±2.2	1.2±0.4	5.42±1.50	−0.13	5.31±1.41	−0.19
	35-60	20	3.5±2.0	2.1±0.6	4.99±1.67	−0.18	5.04±1.20	−0.22
Midfrontal gyrus	65-90	18	4.0±1.8	1.8±0.4	6.04±1.67	−0.18	6.07±1.57	−0.22
	45-65	18	1.9±1.0	1.4±0.5	5.26±1.54	−0.12	5.31±1.61	−0.14
Inferior frontal gyrus	50-70	17	2.6±1.8	1.4±0.6	5.45±1.35	−0.04	5.62±1.42	−0.12
	35-50	20	4.1±2.1	1.8±0.7	5.29±1.35	−0.08	5.44±1.51	−0.18
Orbitofrontal gyrus	20-35	19	7.6±4.8	1.5±0.7	4.64±1.29	0.07	4.74±1.42	0.00
Cingulate gyrus	35-70	21	5.6±4.2	4.6±1.7	5.35±1.30	−0.32	5.29±1.23	−0.28
Precentral gyrus	70-100	18	3.5±2.4	1.8±0.4	6.17±1.72†	−0.32		
	55-70	17	2.0±1.1	1.2±0.4	5.56±1.66	−0.27	5.81±1.64	−0.16
Paracentral lobule	80-100	17	8.0±4.9	2.9±1.0	5.98±1.61†	−0.29		
Parietal lobe								
Postcentral gyrus	70-100	18	3.5±1.8	1.8±0.4	5.70±1.41	−0.23	5.82±1.55	−0.11
	55-70	17	2.4±1.3	1.1±0.3	5.15±1.53	−0.12	5.30±1.64	−0.04
Superior parietal gyrus	70-100	18	7.5±4.5	1.8±0.4	5.53±1.46	−0.18	5.65±1.54	−0.08
Inferior parietal gyrus	45-70	21	10.3±4.3	2.9±1.2	5.01±1.30	−0.16	5.26±1.52	−0.12
Precuneus	65-80	19	4.1±2.2	1.0±0.0	6.23±1.54	−0.17	6.20±1.48	−0.19
Temporal lobe								
Superior temporal gyrus	30-45	21	7.2±4.8	1.6±0.9	4.78±1.18	0.01	4.92±1.32	−0.08
Inferior and middle temporal gyri	15-30	10	7.7±4.5	1.3±0.5	4.45±0.99	0.35	4.84±1.24	0.15
	5-15	15	5.7±2.9	1.0±0.0	3.66±1.04	−0.17	3.66±0.95	−0.41
Hippocampal region	20-35	16	3.7±2.5	1.2±0.4	4.12±1.22	−0.08	4.18±1.27	−0.07
Anterior-medial temporal region	20-35	5	1.3±0.8	1.0±0.0	3.49±0.59	−0.10	3.55±0.56	0.07
Occipital lobe								
Cuneus	45-65	21	3.7±2.1	1.2±0.4	5.83±1.40	−0.05	5.76±1.35	0.02
Calcarine	30-45	21	3.8±2.4	1.1±0.4	5.21±1.11	0.07	5.28±1.24	0.06
Lingual	15-30	18	4.5±2.8	1.1±0.2	4.43±1.27	0.03	4.60±1.30	0.06
Retrosplenial grey matter	45-70	16	2.8±2.1	2.5±0.9	5.47±1.57†	−0.10		
Caudate nucleus	35-55	21	2.9±1.9	1.8±0.5	5.19±1.27	−0.14	5.39±1.51	−0.15
Thalamus	40-50	19	1.3±0.8	1.0±0.0	4.89±1.47	−0.02	4.99±1.40	0.04
Insula	40-60	20	4.6±2.3	1.3±0.4	5.61±1.36	−0.13	5.77±1.62	−0.07
Cerebellum	5-15	16	6.5±4.2	1.3±0.5	4.39±1.18	0.02	4.64±1.28	0.13
Centrum semiovale	70-90	18	0.57±0.28	1.0±0.0	2.83±0.70	−0.15	2.64±0.63	−0.44

*Mean±SD †Midline structure, mean for right and left sides No correlation coefficient was statistically significant ($P > 0.05$) $rCMR_{glc}$ was calculated by Equation 1 (*see* text) The number of slices equals the mean number per brain in which a region was identified, and net area equals the sum of the regional surface areas in slices in which the region was identified

Division of net surface area by mean slice number provides an estimate of the surface area per slice for the region of interest.

rCMR$_{\mathrm{glc}}$ ranged from 2.6 mg. 100 g^{-1}. min^{-1} at the centrum semiovale (white matter) to 6.2 mg. 100 g^{-1}. min^{-1} in the precuneus (grey matter) of the parietal lobe. In none of the 31 regions was rCMR$_{\mathrm{glc}}$ correlated significantly with age, nor was any right/left ratio for rCMR$_{\mathrm{glc}}$ correlated significantly with age at any bilaterally symmetrical region. A grey/white ratio for rCMR$_{\mathrm{glc}}$ was calculated from Table 3 by dividing rCMR$_{\mathrm{glc}}$ at the precuneus by rCMR$_{\mathrm{glc}}$ at the centrum semiovale; both regions occur at the same level above the IOM line. For 19 subjects, this ratio ranged from 1.7 to 3.3; its mean equalled 2.2 ± 0.2 (SD) at the right hemisphere and 2.3 ± 0.5 at the left.

Individual values for weighted rCMR$_{\mathrm{glc}}$ at the right and left inferior parietal gyri, a typical brain region (*see* Table 3), are plotted against age in fig. 3. The slopes of the regression lines are statistically insignificant.

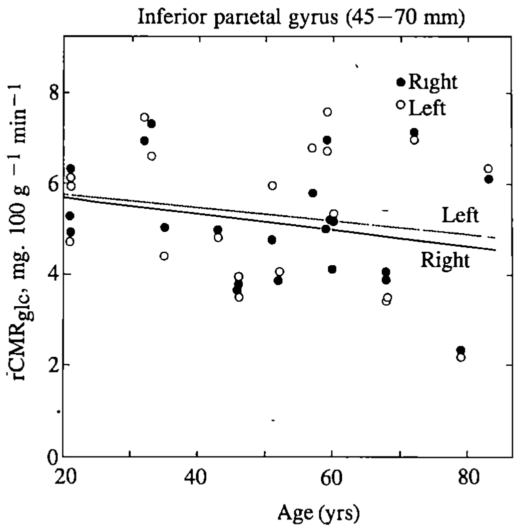

FIG. 3 Relation of regional cerebral metabolic rate for glucose, at right and left inferior parietal gyri, to age, for 21 healthy subjects. The least-squares fits to the data are given in the figure. Their slopes do not differ significantly from 0 ($P > 0.05$).

DISCUSSION

Metabolic rates for glucose in each cerebral hemisphere, in the grey matter of each hemisphere and in bilaterally symmetrical and midline brain regions were not correlated significantly with age in a sample of 21 healthy men, aged 21 to 83 yrs. Furthermore, right/left ratios for the metabolic rates were not correlated with age and did not differ significantly from 1. In view of the variability of the data, however, a larger group of normal healthy men should be examined to generalize the above conclusions.

In agreement with observations that ageing is associated with reduced pulmonary gas exchange (Dastur *et al.*, 1963; Libow, 1963), Pa_{O_2} was correlated significantly and negatively with age in the 21 subjects. We have no explanation for the significant correlations between age and both Pa_{CO_2} and arterial pH. The subjects, who were screened for cardiovascular disease and other conditions that might contribute to brain dysfunction, had a high educational level and high performance and verbal scale scores on the Wechsler Adult Intelligence Scale (Wechsler, 1958). The negative correlation between the performance scale score and age, and the insignificant correlation between the verbal scale score and age, correspond to previous observations on healthy subjects (Birren *et al.*, 1963; Horn, 1975).

Methodological problems necessarily limit conclusions based on PET. CMR_{glc} might be estimated more accurately with white as well as grey matter constants were grey and white matter distributions within each hemispheric slice known, but these are unavailable because of partial voluming effects (Mazziotta *et al.*, 1981*b*). Fortunately, use of either grey or white matter constants provided values for CMR_{glc} which differed by less than 10 per cent, because the operational equation is rather insensitive to the choice of constants when PET is performed 45 min or later after injection of ^{18}FDG (Sokoloff *et al.*, 1977; Phelps *et al.*, 1979).

Errors due to reconstruction, partial voluming and inadequate spatial resolution clearly influence the value of $rCMR_{glc}$. Generally, $rCMR_{glc}$ at grey matter is underestimated and at white matter it is overestimated, the errors being greater in smaller regions of interest (Hoffman *et al.*, 1979; Mazziotta *et al.*, 1981*b*). Errors can be estimated direct from information about the volume and shape of a given region and about resolution properties of a PET scanner (Mazziotta *et al.*, 1981*b*).

The grey/white ratio for $rCMR_{glc}$, at the precuneus as compared with the centrum semiovale, ranged from 1.5 to 3.3 (mean = 2.3 to 2.4), whereas studies in the rhesus monkey suggest that it approximates 3.5 to 4.0 (Kennedy *et al.*, 1978). With the ECAT II scanner, the grey/white ratio for $rCMR_{glc}$ is reported to equal 1.5 to 2.5 (Kuhl *et al.*, 1980; Huang *et al.*, 1980; Mazziotta *et al.*, 1981*a*), and for CMR_{O_2} to approximate 3 (Frackowiak *et al.*, 1980; Lammertsma *et al.*, 1981). This higher value represents the capability of the ECAT II when attenuation coefficients are determined empirically at each point in a PET slice, a procedure not routinely employed (*see* Methods) (Frackowiak *et al.*, 1980). The grey/white ratio for $rCMR_{glc}$ is reported as 0.9 with the PETT III scanner (Ferris *et al.*, 1980) and as 1.8 with the Mark IV scanner (Reivich *et al.*, 1979).

If net regional surface areas in Table 3 are multiplied by 1.4 cm, the distance between the midpoint of successive slices, then net regional volumes of interest can be calculated. They roughly agree with actual anatomical dimensions. For example, calculated volumes of interest equal 1.8 cm^3, 4.0 cm^3 and 378 cm^3 for the thalamus, head of caudate nucleus and cerebral hemisphere between 30 and 80 mm above the IOM line, respectively, as compared with actual volumes of 3.3 cm^3 for the thalamus, 4.6 cm^3 for the caudate nucleus and 545 cm^3 for an entire hemisphere (Blinkov and Glezer, 1968).

For the 21 healthy men, mean CMR_{glc} equalled 4.41 mg. 100 g^{-1}. min^{-1} at the left hemisphere and 4.34 mg. 100 g^{-1}. min^{-1} at the right. These means are somewhat lower than those determined by the direct technique of Kety and Schmidt (1948) in healthy young subjects (6.0 mg. 100 g^{-1}. min^{-1}) and in subjects 20 to 50 years of age

(5.3 mg. 100 g^{-1}. min^{-1}), but approximate to the mean in elderly healthy men, 4.6 mg. 100 g^{-1}. min^{-1} (Dastur *et al.*, 1963; Gottstein and Held, 1979). In other studies with PET, CMR_{glc} has been reported to range from 5.9 to 7.0 mg. 100 g^{-1}. min^{-1} (Reivich *et al.*, 1979; Huang *et al.*, 1980; Mazziotta *et al.*, 1982). However, Kuhl *et al.* (1982) recently reported a mean of 4.7 mg. 100 g^{-1}. min^{-1} in normal healthy subjects 18 to 79 years of age.

Our lower values for CMR_{glc}, as compared to some but not all previously reported values obtained with PET (*see* Kuhl *et al.*, 1982), could be due to sensory deprivation of our subjects, who had their eyes covered and external auditory canals plugged with cotton in the first 45 min following the injection of ^{18}FDG. Visual and auditory deprivation during PET in young subjects reduces CMR_{glc} by up to 40 per cent in perisylvian hemispheric regions containing language areas and in the basal ganglia, and to a lesser degree in other brain regions (Mazziotta *et al.*, 1982; J. C. Mazziotta, personal communication).

CMR_{glc}, $(CMR_{glc})_{grey}$ and $rCMR_{glc}$ were not correlated significantly with age in the 21 healthy men. These observations differ from those of Dastur *et al.* (1963) and Gottstein and Held (1979) that net CMR_{glc}, as determined by the direct technique of Kety and Schmidt (1948), is reduced in elderly subjects. Our findings are consistent with reports that CMR_{O_2} and CBF are age invariant in healthy subjects (Shenkin *et al.*, 1953; Dastur *et al.*, 1963), but not with reports that CMR_{O_2} is reduced in the elderly (Fazekas *et al.*, 1952; Scheinberg *et al.*, 1953; Lassen *et al.*, 1960; Gottstein and Held, 1979).

PET has been employed to examine brain oxidative metabolism in relation to age in two additional studies. Kuhl *et al.* (1982) used PET with ^{18}FDG in 40 healthy men aged 18 to 78 years, and found that hemispheric CMR_{glc} as well as $rCMR_{glc}$ in grey and white matter regions were reduced in the elderly. Similarly, Frackowiak *et al.* (1980) and Lammertsma *et al.* (1981) reported that CMR_{O_2} and CBF, when $H_2{}^{15}O$ and $C^{15}O_2$ were employed as positron-emitting tracers, were significantly reduced in cerebral grey but not white matter of the elderly. The data were re-evaluated recently, however, because several high values for CMR_{O_2} in young subjects were considered to be faulty. When these latter values were ignored, CMR_{O_2} was found to be independent of age, whereas CBF remained reduced in the elderly (R. S. J. Frackowiak, personal communication; Frackowiak, 1983). Because the arterio-venous concentration difference for O_2 was elevated in the older subjects, the results suggested that they had cerebrovascular disease without metabolic impairment (*see* O'Brien and Mallett, 1970).

Some previous reports of a reduced cerebral oxidative metabolism in the elderly may have been due to inclusion of subjects with cerebrovascular disease (Resch and Baker, 1964; Kety, 1956; Gottstein and Held, 1979). Furthermore, most studies were performed with unregulated sensory stimulation, and it is known that visual and auditory faculties decline in the elderly (Weiss, 1963; Ordy and Brizzee, 1979; Devaney and Johnson, 1980; Grady *et al.*, 1982) and that sensory deprivation in the young can reduce CMR_{glc} and $rCMR_{glc}$ (Mazziotta *et al.*, 1982). Thus, some reported age reductions might have reflected functional decrements in visual and auditory inputs to the brain, rather than intrinsic brain ageing. Further research is required to evaluate this latter possibility.

Brain weight falls by about 10 per cent between 20 and 80 yrs of age (Minkler and Boyd, 1968; Blinkov and Glezer, 1968), up to 50 per cent of neurons die in selected brain regions, and many remaining neurons become pathological (Critchley, 1942; Brody, 1955; Ball, 1978; Scheibel, 1978; Henderson *et al.*, 1980). Furthermore, enzymes involved in neurotransmitter synthesis show age-related decrements (McGeer and McGeer, 1976), and intelligence as measured by the performance scale score of the Wechsler Adult Intelligence Score, declines with ageing (Birren *et al.*, 1963) (Table 1).

The constancy of $\mathrm{CMR_{glc}}$ and $\mathrm{rCMR_{glc}}$ with age, despite these morphological and functional decrements, might reflect the fact that the metabolic rates are intensive rates per g tissue. If the net volume of a brain region, such as the thalamus, were reduced in the elderly (Schwartz *et al.*, 1983), then metabolism for the region as a whole might be reduced even though metabolism per gram of region were not. Obviously, information concerning regional brain volumes during ageing is necessary to examine this issue.

Constancy of the rate of glucose utilization with age also might be due to the fact that the subjects were examined under resting conditions. Age deficits might be evident if the brain were subjected to pharmacological or physiological stimulation (Rapoport *et al.*, 1983). For example, although $\mathrm{rCMR_{glc}}$ does not change during senescence of the Fischer-344 rat, the metabolic response to oxotremorine, a muscarinic cholinergic agonist, is less in many brain regions of senescent than of mature rats (London *et al.*, 1982).

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NOTICES OF RECENT PUBLICATIONS

Diseases of the Nervous System. By W. B. Matthews. Fourth Edition. 1982. Pp. 415. Oxford: Blackwell Scientific. Price £12.00.

Admirers of Professor Matthews' impeccable English prose style will be alarmed to see his latest textbook of neurology described on the cover as demystifying. After a few pages, however, they will be reassured that nothing has changed. The approach is comfortably traditional and apart from an occasional lapse such as the use of the phrase 'facial hemispasm' (for hemifacial spasm) the master's touch is as sure as ever. The basic physiology is admirably summarized in the first chapter although recent advances in neurochemistry get scant attention. Thereafter the book is entirely clinical and achieves its purpose admirably. The descriptions of disease, advice on management and prognosis are all models of clarity and now that the powerful influence of the original senior author has passed, his individual views on such conditions as the posttraumatic syndrome have been modified. The illustrations, however, are disappointing, even for a students' inexpensive edition. The diagram of the visual pathways confuses the disc and fovea (fig. 5), the spinothalamic tract disappears somewhere between the cord and medulla (fig. 2) and fig. 7 labelled 'unmistakable paralysis of the left side of the palate' is so dark as to be unrecognizable.

These are small criticisms of an admirable text which can be thoroughly recommended to all students as readable, informative and accurate.

R. W. ROSS RUSSELL

Cancer and the Nervous System. The Neurological Manifestations of Systemic Malignant Disease. By R. A. Henson and H. Urich. 1982. Pp. 657. Oxford: Blackwell Scientific Publications, Oxford. Price £35.00.

Although neuro-oncology is regarded as a relatively new and rapidly expanding branch of the neurological sciences, for the past thirty years the workers at the London Hospital—the late Lord Brain, Dr Henson, Professor Urich and their colleagues—have been carefully, systematically and painstakingly studying the neurological manifestations of malignant disease in thousands of patients. The present book is the culmination of their work and a testimony of their vast clinical and pathological experience. Although most of the authors' previous published work in the field has been concerned with the remote or paraneoplastic effects of malignancy, the book also deals extensively with direct involvement of the nervous system by carcinoma, lymphoma and other reticuloses. Primary tumours of the nervous system are deliberately excluded from consideration.

The book is divided into three parts. Part I, after a brief introductory chapter on epidemiological aspects of malignant disease, deals with direct involvement of the nervous system by carcinoma. There are chapters on metastases to the brain and the effects of neighbouring tumours such as those of the skull and nasopharynx. Carcinomatous meningitis receives separate consideration. There are also chapters on the involvement of the vertebral column and spinal cord. Throughout the book the authors provide many interesting clinical examples from their own experience, such as a most unusual case of carcinoma of the stomach with diffuse infiltration of skeletal and extraocular muscles by tumour deposits.

In Part II, on direct involvement of the nervous system in the reticuloses, the effects of Hodgkin's and non-Hodgkin's lymphomas, leukaemias, multiple myeloma and polycythaemia vera are considered. In the final section, Part III, on paraneoplastic conditions the authors bring together their own original work and that of others on the remote effects of malignancy. There are separate chapters on encephalomyelitis, cerebellar degeneration, peripheral neuropathy, and muscular and neuromuscular disorders. In addition there are excellent chapters on infections, nutritional and endocrine disorders and the unwanted effects of treatment especially radiation and cytotoxic drugs.

The vast experience of the authors shines through each chapter of this excellent book. Every aspect of the malignancies has been thoroughly researched and well referenced. It is an authoritative work which will become a standard reference on the subject since it brings together information that cannot readily be found elsewhere. This excellent publication, which is profusely illustrated with photographs of pathological sections is highly recommended to all neurologists, neurosurgeons and others concerned in the management of patients with cancer of the nervous system. The price is very reasonable.

J. G. MCLEOD

The Neuropsychology of Cognitive Function. Proceedings of a Royal Society discussion meeting organized and edited by D. E. Broadbent and L. Weiskrantz. 1982. Pp. 226. London: The Royal Society. Price £27.80.

Since the last war, the interests of neurologists and psychologists have converged to produce the now well-established discipline of neuropsychology. The ever-accelerating pace of research in neuropsychology has been paralleled by its ever-widening scope. It seemed, therefore, to the organizers of the symposium which this publication reports, that the time was ripe to review the field and take stock of the achievements of contemporary neuropsychology. Since it is arguable that the brain reveals its mode of organization most clearly when it is damaged or diseased, it is not surprising that the major contributions to neuropsychology still come from studies in which the effects of damage or disease on cognitive functions are carefully assessed. What is *abnormal* functioning of the brain can, however, only be properly understood against the baseline of an adequate understanding of the *normal* functioning of the brain. Thus, there is a kind of template of information about normal psychological processes against which theories of abnormal functioning must be set and tested.

Around the common theme of the neuropsychology of cognitive function, the symposium gathers a diversity of contributions which can be classified along a number of different dimensions. Thus, the type of papers presented differs from chapter to chapter. On the one hand, there is the overall review type exemplified by the contributions of Milner and Paillard. Whilst Milner reviews the work over the past quarter century on selected aspects of frontal lobe function, Paillard reviews work on apraxia and the neurophysiology of motor control. Both of these papers are heavily documented and cite numerous references to work in the field. By contrast, other contributions, notably that of Geschwind, are much more informal, indeed chatty (not to say rambling and repetitive at times) in style. He is nevertheless, as always, highly provocative in indicating possible fruitful areas for future research in neuropsychology. The contrast between contributions such as Geschwind's and those of Paillard and Milner is exemplified by the number of references each gives. Whilst Paillard cites more than a hundred references, Geschwind cites a mere seven. Other contributions are neither reviews nor highly speculative but concentrate on recent advances in a relatively circumscribed area. Examples of this type of contribution are the chapters by Posner on the control of spatial orientation and Coltheart who starts from theoretical issues in psycholinguistics and argues for their relevance in understanding disorders of language. The limited coverage given to language in the volume as a whole is explained by the fact that a joint meeting of the British Academy and the Royal Society was held on language only seven months earlier.

The diversity in style of contribution is matched by a similar diversity in content. Thus, the contribution by Cowey on sensory and nonsensory visual disorders in man and monkey leans heavily upon careful experimental studies in nonhuman primates, whereas the contribution by Mishkin deals almost exclusively with evidence for a memory system in the monkey. Other papers deal with the results of brain damage in humans, whilst yet others concentrate almost entirely upon normal psychological functions and only refer to abnormal functioning as it helps to understand normal psychological functioning. Such, for example, is the contribution by Baddeley on implications of neuropsychological evidence for theories of normal memory, and Marshall who discusses biological constraints on orthographic representation. Across this subdivision of animal *versus* human papers, there runs the further subdivision of mainly experimental *versus* clinical type studies.

For the busy neurologist and neurosurgeon who wish to have an authoritative and relatively brief overview of what is happening in neuropsychology today, this volume is to be highly recommended. Whilst the researcher intimately involved in neuropsychological work will find some of the chapters useful at pulling together the important contributions in particular areas of neuropsychology, he will feel at times that other chapters cover ground more than adequately covered elsewhere. Psychologists reading this volume will be surprised, and perhaps disappointed, not to find a chapter on a topic which, rightly or wrongly, has preoccupied a good deal of the thinking and publishing in neuropsychology for a decade. I refer to studies of cerebral asymmetry of function. A really extensive and highly critical review of this area would have been a most welcome contribution to the symposium. There is so much folklore circulating on this topic at the moment that such a contribution is sorely needed. Also, having in mind the enormous impact that the work of Sperry and his associates on the neocortical commissures made on the whole field of neuropsychology for a quarter of a century, it is surprising to find little or no reference to it in a volume of this kind. The initial emphasis on the information transmitting and integrating functions of the neocortical commissures tended to overshadow other, arguably equally important, functions of these commissures for the development and maintenance of normal psychological functioning. It is a pity that this particular topic was not treated in the symposium. No doubt another reviewer would highlight other gaps in what is covered, since, to some extent, it must remain a matter of personal preference.

Although the quality of the separate chapters varies enormously, there are more than enough high quality contributions to have justified the holding of the symposium and it will remain an important milestone along the pathway of the development of neuropsychology.

M. A. JEEVES

Acquired Aphasia. Edited by M. T. Sarno. 1981. Pp. 537. New York and London: Academic Press. Price £19.60; $29.50.

Aphasia. By F. L. Darley. 1982. Pp. 285. Philadelphia: W. B. Saunders Company. Price $24.00.

The past decade has witnessed significant changes in the study of acquired language disorders and a spate of books documenting these changes. The main new inputs into this study have come from linguistics, psycholinguistics (as part of cognitive psychology) and neuropsychology. These two books, both from internationally respected speech-language pathologists in the USA, complement and contrast with each other in the use they make of these new inputs.

Darley's book, entitled *Aphasia* but restricted in its topic entirely to the subject of acquired aphasia in adults, is a complement to the classic book on the dysarthrias which he coauthored in 1975, *Motor Speech Disorders*. He writes from a wide experience of rehabilitation of aphasic patients, and draws on an extensive survey of the American literature on speech and language pathology, but makes few references to the studies recently undertaken by European linguists, psychologists and neurologists. His interpretation of aphasia is in the tradition of Marie, Schuell and Wepman, namely, that aphasia is a supramodal reduction of language which is essentially homogenous in character and is, as he summarizes it, 'aphasia without adjectives'. With this kind of viewpoint, the book shows little interest in the neuroanatomy or neurophysiology of aphasia. Nor does it share the current enthusiasm of psycholinguists for examining aphasia as a means of fractionating the mental processes involved in producing and receiving spoken and written language. Indeed Darley uses the psycholinguistic studies of agrammatism by Goodglass, Zurif and others in support of his claim that aphasia is unitary, although these researchers themselves interpret their studies as providing evidence for the existence of different types of aphasia. Darley's ultimate justification for his viewpoint is that of many speech pathologists and therapists, the pragmatic claim that some common principles of treatment are appropriate for all aphasic patients. The validity of this justification depends of course on the certainty that the treatment is apt and Darley devotes the major portion of the book to a description of the principles and procedures he advocates in therapy, including chapters on recovery from aphasia and the assessment of aphasic patients. Consistent with the unitary interpretation of aphasia, the recommendations for therapy are those based on maximizing verbal stimulation first expounded by Schuell in the 1960s, but now supplemented with recent explorations of the effects of timing of stimuli, selection of input modality, information overload, etc. The chapters on the natural course of recovery from aphasia and the evaluation of treatment provide the most comprehensive surveys of these topics currently available. Speech therapists, always sensitive to the need to justify the time they spend on aphasia rehabilitation, will derive some comfort from Darley's catalogue of studies of the effectiveness of treatment, with and without no-treatment control groups or using individual case studies of patients with chronic aphasia.

Whereas Darley's book provides a good introduction to this perspective on aphasia suitable for undergraduate students of psychology or speech pathology, *Acquired Aphasia*, edited by Sarno, is both broader and deeper in scope. Its bias is towards the analysis of aphasia by syndrome and it will have more to offer to the neurologist, neuropsychologist or speech pathologist who already has some familiarity with surveys of aphasia. The breadth of scope is evident from the contents page. It encompasses aphasia in children, in the head-injured and in the elderly. The relationships of aphasia to intelligence, artistry and emotion are considered. There are surveys of clinical aphasia tests and of rehabilitation. The study of aphasia is set, by Benton, in a historical perspective which begins in 1700 BC but does less than justice to the processing models of current psycholinguistic investigations. The chapters by H. and A. Damasio on the syndromes of aphasia and their cerebral localization accept uncritically the Boston classification of the aphasias into Broca's, Wernicke's, conduction, transcortical sensory, transcortical motor, anomic and global aphasias. Using the method of cumulative overlap of lesion sites from CT scans, despite its limitations, H. Damasio plots the cerebral localization of these syndromes, repeating such classical statements as 'Broca's aphasia is associated with lesions of the left frontal lobe which generally involve Broca's area' without sufficiently emphasizing that current examinations of these syndromes indicate that much finer behavioural divisions are needed. 'Broca's aphasia', for example, generally subsumes some (but probably not necessarily all) of the components of apraxia of speech, agrammatism in speech which may be structural and/or morphological, and agrammatism in comprehension. The indications are that lesions limited to Broca's area disturb the articulation of speech but not the production or comprehension of grammar. The chapter by Kaplan and Goodglass, on aphasia-related disorders, disappointingly for these authors, limits itself to the classic clinical syndromes of disorders of reading and writing, skimming also over apraxia, acalculia and the Gerstmann syndrome: current psycholinguistic studies of reading disorders are only briefly acknowledged by a reference to deep dyslexia, but with no mention of the many other processing disruptions of reading which have been proposed.

Despite this somewhat pedestrian rehearsal of clinical lore in some of its chapters, other chapters discuss some stimulating controversies in the psycholinguistic study of language disorders. These are, notably, the chapters by Blumstein on phonological aspects of speech production and perception in aphasia, Berndt and Caramazza on grammatical deficits in aphasia and Buckingham on word-retrieval problems. One of Blumstein's main themes is that deficits in auditory language comprehension are not necessarily secondary to deficits in speech perception such as impairment in the processing of rapid acoustic events. Berndt and Caramazza are advocates of the view that the agrammatic speech of Broca's aphasia reflects a central disorder involving comprehension as well as production; they reject the claim that the difficulty Broca's aphasics experience with grammatical words is due to the latter's lack of phonological stress, pointing out that they have difficulty also in producing adjective-noun combinations where all the words carry stress. Buckingham distinguishes the various problems of word-retrieval in aphasia as resulting in hesitations, blocking, semantic paraphasias, unrelated paraphasias, indefinite anaphors ('thing', 'it', etc.) or neologisms ('new' words). He describes four ways in which neologisms could arise, namely, through a random-phoneme generator, through perseveration of earlier sounds, from a combination of semantic misselection and phonemic misselection, or through phonemic misselections so extreme that a 'word' which has been retrieved from the mental lexicon is changed out of all recognition when uttered. Buckingham's other chapter, on explanations for the concept of apraxia of speech, also makes good reading, although it is essentially a repeat of his 1978 paper in *Brain and Language*. It concerns predominantly the neurological interpretaion of apraxia as secondary either to disconnection of verbal input from motor association areas or to lesions in the cortical centres themselves. In the latter interpretation, apraxia of speech is equivalent to a limb-kinetic apraxia. Buckingham's perspective is also that of a linguist, however, and he cautions against the assumption that the abstract linguistic notion of 'phoneme' can be directly translated into neural motor commands for speech production. His review of phonetic studies of voice-onset-time in apraxic speech ends by emphasizing the need for such detailed examination of speech errors to complement clinical behavioural studies.

In a rapidly developing field it is not surprising that there are omissions in this book's survey of adult aphasia, for example PET and rCBF studies of aphasic patients, psycholinguistic dissociation studies of dyslexia and dysgraphia, holographic and matrix models of word-retrieval as applied to aphasia and neuropsychological approaches to treatment. Nevertheless there is ample enough stimulating reading here about this frontier for brain-behaviour research to make the concluding sentence of Berndt and Caramazza's chapter a fitting commentary for the whole book: 'Although these suggestions must be approached with caution, they present the growing number of psychologists, linguists, neurologists and speech pathologists who are interested in aphasia with exciting prospects for future research.'

RUTH LESSER

Correlative Neurosurgery. Edited by Richard C. Schneider, Edgar A. Kahn, Elizabeth C. Crosby and James A. Taren. Third Edition. 1982. Volumes 1 and 2, pp. 1669. Springfield, Ill.: Thomas. Price $225.00.

Correlative Neurosurgery was originally written by a number of associates and trainees of Dr Max Peet at the University of Michigan. Deriving an interest in correlating the clinical practice of neurosurgery with neuroanatomy from Dr Peet himself, it took the form of reviewing neurosurgical topics in parallel with accounts of the relevant aspects of neuroanatomy. The initial conception and much of the basic material of the book have been retained, but since the second edition was published in 1969, it has been expanded enormously. The second edition was contained in a single volume and ran to 693 pages. The third edition has grown to 1669 pages and two volumes, each of which is rather too large to be handled with comfort. The 37 contributors to the new edition are still, for the most part, associated with the University of Michigan.

A book which has reached this size must now be judged by its efficiency as a general neurosurgical textbook. On the whole it passes the test. It has been brought up to date by the provision of many entirely new chapters covering such subjects as CT scanning, evoked potentials, radiotherapy and chemotherapy in the management of intracranial tumours, neuroendocrinology and acoustic neuromas. Much of the book is excellent and may be read with profit and enjoyment by the experienced neurosurgeon as well as by the younger man at the end of his training for whom it was originally intended. Amongst the first rate chapters may be noted those on cerebral tumours and the chapter on injuries and defects of the scalp. The standards of production, printing and illustration are as high as we have come to expect of North American specialist books. The lists of references are fuller than in the last edition and for most chapters have been brought up to date. This reviewer must, however, express some reservations about the balance of the book in relation to the realities of everyday neurosurgery.

First, the original conception probably exaggerated the importance of a certain type of detailed neuroanatomy in surgical work. The clinical neurosurgeon needs relatively little knowledge of the type of tract-connection anatomy that is dear to the professional anatomist, being more concerned with the detailed arrangement of structures on the surface of the brain that receive little attention in the anatomical textbooks—the relationship of vessels, arachnoid, dural partitions and so on, that he encounters in clipping an aneurysm or removing a basal tumour.

Secondly, the amount of space allocated to some of the topics in the book is difficult to justify. Thus, stereotactic surgery and the surgery of epilepsy are discussed at great length, while only 34 pages are devoted to intracranial aneurysms and arteriovenous malformations. Subarachnoid haemorrhage now constitutes one of the major fields of interest for almost all neurosurgeons, whilst stereotaxis and epilepsy surgery have become the preserve of a tiny number of ultraspecialists, to such a degree that the general neurosurgeon needs to know no more than the guiding principles in these fields.

Despite these reservations, however, it must be said that this new edition of *Correlative Neurosurgery* contains much of value and interest and suffers from no more flaws than are inevitable in a very large multiauthor work. Its purchase is strongly recommended to those libraries and neurosurgeons whose means are sufficiently ample to bear the cost without distress.

R. S. MAURICE-WILLIAMS

Substance P in the Nervous System. Ciba Symposium 91. 1982. Pp. 349. London: Pitman. Price £25.00.

One of the activities of the Ciba Foundation is to organize international multidisciplinary meetings on biomedical and chemical topics of current interest. Attendance at the meetings is usually limited to a small number of invited participants, but the proceedings are published soon after the meetings to make the results available to a wider audience. This volume represents the proceedings of the Ciba Foundation Symposium held on substance P in December, 1981 and maintains the high standards already set by Ciba publications. The book has 18 chapters with contributions from many of the leading laboratories working in the field and most of the chapters are a successful mixture of general review and new research data. The prestige of the Ciba Foundation has probably helped to keep the standard of the contributions high and to make the volume more valuable than the average published symposium proceedings.

The book opens with introductory comments by the chairman of the Symposium (Burgen) and a stimulating overview by von Euler of changing concepts of chemical transmission. The main chapters cover aspects of substance P synthesis (Keen *et al.*) and inactivation (Lee), receptor classification (L. L. Iversen *et al.*) and distribution (Cuello *et al.*, Hökfelt *et al.*). Specific neuronal systems which are covered include the sensory neuron (Otsuka *et al.*, Lembeck and Gamse) and its relationship to pain transmission (Henry, Jessell, Wall and Fitzgerald), substance P interactions with dopaminergic neurons of the substantia nigra (Glowinski *et al.*) and ventral tegmental area (S. D. Iversen) and the substance P-containing neurons of the gut (Costa *et al.*). There are also chapters on the modulation of cholinergic transmission at Renshaw cells by substance P (Ryall), the regulation of substance P expression and metabolism (Black *et al.*) and the relation of substance P to stress and catecholamine metabolism (Oehme *et al.*). Each chapter is accompanied by an annotated transcript of the discussion which followed the original presentation of papers at the symposium and the book closes with a general discussion. For the reader who is heavily involved in substance P research the discussion sections are fascinating because they serve to highlight the areas of knowledge which are either controversial or inadequately studied. The discussion sections also provide a means of assessing how the work described in individual chapters is received by other experienced workers in the field.

Although the title of the book is rather general, not all aspects of substance P in the nervous system are given equal coverage. For example, there is disappointingly nothing on the distribution of substance P in the human brain or on the relationship of substance P to diseases such as Huntington's chorea. Apart from the chapters by Glowinski *et al.* and Cuello *et al.*, there is also relatively little about the striatonigral substance P-containing system. In contrast, the substance P-containing primary afferent system is dealt with in great detail and it appears to be the substance P neuronal system which is most researched and best understood. The paper by Lembeck and Gamse summarizes the now quite compelling evidence that substance P at peripheral endings is involved in antidromic vasodilatation and the axon reflex. However, although eight of the chapters touch on the role of substance P at the central terminals of sensory neurons, it is clear that there is still not a consensus of opinion as to whether substance P is the main excitatory transmitter of small diameter primary afferent fibres (*see* especially the chapter by Wall and Fitzgerald), nor is the precise mode of substance P modulation by enkephalin understood. The role of substance P at the central and peripheral endings of primary afferent fibres relates also to two other prominent themes in this symposium. First, several chapters cover recent evidence that substance P in sympathetic ganglia is released from the collaterals of visceral afferents and has a transmitter function (Otsuka *et al.*, Cuello *et al.*, Hökfelt *et al.*). Secondly, parts of chapters and much of the discussion focuses on the coexistence of substance P with other putative transmitters and its possible functional significance (von Euler, Hökfelt *et al.*, Wall and Fitzgerald, Ryall). Another theme covered in the book is the action of substance P antagonists. Although there is no chapter devoted to antagonists, several of the discussion sections report preliminary results with antagonists and it is hoped that their use will serve to clarify some of the presently conflicting or confusing results.

It is five years since the publication of the last symposium book on substance P (*Substance P*, Nobel Symposium (1977), Raven Press). This book provides a summary of the progress which has been made in that time and should be useful for those who are not already familiar with the literature. For those working in the field it can be recommended as a convenient reference book and a source of provocative pointers to future research.

J. V. PRIESTLEY

Neurotransmitter Interaction and Compartmentation. Edited by H. F. Bradford. NATO Advanced Study Institute Series. 1982. Pp. 839. New York and London: Plenum Press. Price $95.00.

This extremely large volume represents the proceedings of a ten-day NATO Advanced Study Institute held in Wales during the summer of 1981. As a member of the programme committee, I must immediately confess to being at least in part responsible for the scope, if not the actual content of the book! Due to its size and scope (839 pages, and 52 separate contributions), it is hardly feasible to provide the reader of this review with a detailed synopsis of what lies between the covers. So, in rather more general terms, what might be seen as the good and bad aspects of this book? First, the cost of the book, in spite of its size, is likely to deter all but the libraries—if they can still afford the indulgence of purchasing symposium proceedings. The style and quality of writing is inevitably uneven, with a mixture of excellent reviews providing perspective and new insights, and others that are truly mediocre. Once again, a camera-ready format has been used by the publishers, presumably to speed publication. Why then has it taken so long to appear? As might be expected, there is a plethora of type formats, and the majority used are almost guaranteed to provide the reader with acute eye strain, if nothing else. A semimatt paper is used throughout, which although fine for the text, does not do justice to the micrographs, which suffer from loss of detail and an overall fuzzy appearance.

These criticisms of the book, however, pale into insignificance when one encounters the index. While the editor has made a very reasonable attempt at this arduous task, this vital section of the book has been rendered completely useless by the publishers: the indexed page numbers bear absolutely no relationship to the content of the text itself!

On the good side of things, it can be said that in a single volume, one is provided with a rich source of reference material, notwithstanding its inaccessibility through the index. The arrangement of the book into seven sections, *viz.* nerve terminal organization, factors in neurotransmitter synthesis and release, neurotransmitter interactions, metabolism, isolated cells and tissue compartments, neurotransmitters in subtypes of the brain, and neurotransmitters in the retina, provides for quite good coherence.

The best contributions, to my mind, are those which are not just a rehash of previously published work, or which are limited solely to the material covered by a rather short lecture at the meeting. Some of the most valuable and well-written include chapters by Gray, on nerve terminal ultrastructure; Cotman *et al.*, on the biochemistry of synaptic membranes; De Lorenzo, on calmodulin; Whittaker and Roed, on vesicle cycling mechanisms; two lucid chapters by McGeer *et al.*—one on cholinergic, and the other on GABA systems in the CNS; Hamberger *et al.*, on compartmentalization of glutamate; Clark, on acetylcholine synthesis; Chan Palay, on immunocytochemistry of the cerebellar GABA system; Andersen and Kelly, in their contributions on hippocampal physiology and pharmacology; and, in the retinal section, Ehinger, on morphology and role of monoamines and amino acids in neurotransmission, followed by an excellent review of pathways by Miller *et al.* There are other good chapters, but these I found the most readable and stimulating.

In addition to the full chapters, there are included several short (1 to 2 page) reports, arising from posters presented at the meeting in Wales. Although one can see the reasons for their inclusion in the book, they are really of very limited value, and would have been better omitted.

Finally, a philosophical point, which I guess most scientists must consider from time to time: do published proceedings contribute much (apart from bulk) to the literature? They certainly could, but, I am afraid, frequently do not. Too often, a short contribution in camera-ready form is demanded from speakers at symposia, irrespective of how many times the work has been published elsewhere. Constraints of time and page space rarely permit an author to produce a really incisive or thought-provoking article. Rapid publication, irrespective of quality, is frequently the case. This volume is better than many in this respect, and there are sections of interest to everyone working in the field of neurotransmission. Professor Bradford has done a good job in pulling everything together; however, if faced with the decision of how to spend $95 from my library budget, I doubt whether it would be on this book.

PETER J. ROBERTS

The Biochemical Basis of Neuropharmacology. 4th Edition. By Jack R. Cooper, Floyd E. Bloom and Robert H. Roth. 1982. Pp. 367. Oxford University Press. Price £18.50 (hardback); £7.95 (paperback).

Since this volume first appeared in 1970 it has become well established as the best introductory text available for those who want to learn about the application of biochemical approaches to the study of neurotransmitter and drug actions in the nervous system. This has been a rapidly developing area of research during the past decade, and the authors have done particularly well in keeping their book up to date, as witnessed by the fact that this is already the Fourth Edition in a period of less than twelve years, and the book has grown from 220 pages in 1970 to 367.

As in previous editions, the volume provides a brief introduction to the neurobiology of synaptic transmission in the mammalian CNS, and general reviews of brain metabolism and of the study of neurotransmitter and drug receptors. The latter includes an up-to-date and useful critique of the now popular use of radioligand binding techniques for receptor studies. In the main part of the volume there follows a series of chapters which deals with individual neurotransmitters and related substances. Each chapter gives an excellent and balanced review of what is known about the anatomical distribution, metabolism, and neuropharmacology of particular neurotransmitters and how this knowledge helps in understanding drug actions.

Although the monoamines—acetylcholine, the catecholamines and 5-hydroxytryptamine—are generally recognized to be relatively minor neurotransmitters in CNS it is inevitable that they should dominate this volume (with more than 160 pages) as so much research effort has concentrated on this group. It is a sign of the times, however, that the amino acid transmitters and the nonopioid and opioid peptides in brain should now warrant three separate chapters and a total of some 100 pages, compared with the less than 30 pages assigned in the First Edition.

The volume is well illustrated and produced, and can be thoroughly recommended to all who are interested in this area. Although addressed primarily to a student audience, the volume will be useful even to the expert as a means of keeping abreast of developments in a scientific field that has moved at almost breakneck speed in recent years. It is a pleasure to be able to give this book unreserved praise.

LESLIE L. IVERSEN

Cranial Computed Tomography. By Seungho Howard Lee and Krishna C. V. G. Rao. 1982. Pp. 723. New York and London: McGraw-Hill. Price £64.95.

Ten years have passed since the introduction of computerized tomography, and the rate at which important clinical information is accumulating has slowed. It is therefore to be expected that a number of comprehensive texts will soon appear: this is one of the first.

A team of 20 contributors, some of whom are internationally recognized experts, maintains a generally high standard, and much recent work on CT in diagnosis and management is included The first chapter, on physics and instrumentation, is irrelevant to most of what follows, and might well have been omitted, particularly as it perpetuates confusion in areas such as the meaning of pixel and voxel, and the relationship between Hounsfield and EMI units. Some of the subsequent 16 chapters on different anatomical areas or types of pathology are less comprehensive than the majority: those on white matter disease and diagnostic pitfalls could profitably have been expanded, while the review of 'future expectations' which forms an epilogue is superfluous and perfunctory.

The illustrations, numbering over 600 (many being multiple) are mostly good and well produced, but a few, not necessarily of rare conditions, are of poor quality.

The editors have not ensured a uniform style, and repetition has not been avoided. Chiari malformations, for example, are dealt with at length (with 27 illustrations) in the chapter on anomalies; later a different author refers to this section, but proceeds to recapitulate much of it, adding a further 8 pictures. It hardly seems desirable to devote about one twentieth of the book's illustrations to this one condition.

Other shortcomings are more serious. All the authors are radiologists, and the lack of clinical input is noticeable. Some of the statements from the ivied radiological tower are quite unacceptable: 'Volumetric indices derived from CT can be utilized in identifying dementia . . . other methods of quantifying dementia by means of CT include measuring the mean Hounsfield number in the centrum semiovale.' Would the authors attempt to identify or quantitate pleuritic pain or a rub from measurement of an effusion seen on a chest film?

The bibliography follows the familiar transatlantic approach, concentrating almost exclusively on American publications. This leads to the positive statement 'very few reports have appeared' on megalencephaly, when a major British series is not cited, and to a paragraph based on two pairs of patients with Wilson's disease, ignoring a considerably larger series from France. There are 60 densely printed pages of references (apparently free of interference by authors, proof readers or editors), but of 5 citations in languages other than English, only one is a paper published since 1956.

Furthermore, the attitude to the literature is one of transmission, not assessment; it is largely uncritical.

Readers who care about language will be infuriated. The second paragraph of the authors' preface itself opens with a plural subject and a singular verb, and sets the tone for too much of the book. Jargon abounds: must doctors really write 'the pediatric age group' for 'children' and 'craniocerebral trauma' for 'head injury'?

Such considerations are, however, secondary to the book's merit as a comprehensive text, and at present it must represent one of the best single volume guides to diagnostic CT. If it seems churlish to hope that it will not retain that position, it must be added that it has set a reasonably high standard for prospective challengers.

IVAN MOSELEY

Computer Reformations of the Brain and Skull Base. Anatomy and Clinical Application. By R. Unsöld, C. B. Ostertag, J. DeGroot and T. H. Newton. 1982. Pp. 234. Berlin: Springer. Price DM 280.00.

Sectional images of the brain can now be made by the machine computer in planes which are appropriate for the solution of particular clinical problems from high resolution computed tomogram sections produced in a different plane, usually the standard transverse axial, convenient for scanning. This book contains an atlas of beautifully prepared anatomical sections of the brain and skull base made along axes appropriate for the demonstration of particular structures, especially those features which are visible on high resolution computed tomograms, together with juxtaposed comparable CT images. Detailed case reports show how such selected planes can be used to demonstrate to advantage the pathological basis of disordered function of individual structures.

The atlas forms a complete work in itself and is without references; there are two useful separate indexes based on clinical findings and anatomical features, respectively.

The anatomical sections will be equally valuable for interpretation of sectional images produced by any other radiological method such as nuclear magnetic resonance. The functional clinicoanatomical approach makes the book interesting and instructive reading for clinicians as well as radiologists involved in the elucidation of neurological problems.

BRIAN KENDALL

Physiology and Electrochemistry of Nerve Fibres. By Ichiji Tasaki. Biophysics and Bioengineering Series, Volume 3. 1982. Pp. 348. New York and London: Academic Press. Price not stated.

Professor Tasaki is noted for the pioneer role he has played in elucidating key aspects of the mechanism of nervous transmission in myelinated and unmyelinated fibres. In this monograph, which recapitulates the most important features of his now classic work, *Nervous Transmission*, published in 1953, he traces the conceptual development of this subject and in so doing places more emphasis than perhaps has been the case in recent years on the physico-chemical properties of excitable membranes. As he reminds the reader most pointedly, the historical evolution of ideas pertaining to the electrical excitability of nervous tissue is closely linked with that of electrochemistry so that many physicists of the last century, for example Helmholtz and Nernst, contributed to both fields of knowledge, with the obverse also being the case, since several discoveries by biologists were to have important repercussions for the field of physics. Tasaki also notes that with the advent of electronics, the language of the electrical engineer—positive feedback, gates, channels and equivalent circuits—now determine the principal conceptual framework for the comprehension and manipulation of the phenomena of nervous excitability.

The above remarks provide a clue to the shape of this monograph, one which gives more emphasis to the physicochemical than to the electrical description of membrane excitability. This of course reflects the new methodologies that in recent years Tasaki has utilized to study membrane properties among which measurements of light absorption, birefringence and spectral analysis of the fluorescence responses of excited membranes have figured prominently. The addition of chapters on these topics and others concerned with the internal perfusion of axons and the measurement of 'miniature' potentials as threshold phenomena, clearly distinguish this new monograph from the old and also reveal that Tasaki has not abandoned the electrophysiological approach. Furthermore, the progressive and extended treatment made possible in monograph form allowed one better to comprehend the viewpoint which Tasaki had advanced in his original papers. Thus again in pioneering spirit, Tasaki has followed Katchalsky's precept that 'we must be bold and free in setting forth our ideas' by advancing what he describes as a new theory of nervous excitation, based primarily on a physicochemical description and one which differs from the Hodgkin-Huxley theory, which continues to dominate current thinking.

The membrane is conceived as a mosaic of domains of excitable membrane each containing macromolecules essential to the excitation process. A domain can exist in one or other of two stable states as reflected in the conductances displayed towards monovalent cations (e.g. Na^+, K^+). These states are controlled by the physicochemical properties of the membrane macromolecules. For the 'resting' state the conformation of these macromolecules depends on the presence of semimobile divalent cations (Ca^{++}) which, on displacement by more mobile monovalent ions from the surrounding medium (internal and external), transform a domain to the 'active' state. From the phenomena of bistable states (disclosed originally by his axon perfusion experiments) and the occurrence of 'miniature' electrical responses demonstrated with threshold stimuli (which he emphasizes are effectively eliminated in voltage clamp experiments), Tasaki accounts for the graded (voltage-sensitive) properties of a membrane in terms of that fraction of it which is in the 'active' state. In the Hodgkin-Huxley formulation, graded properties are represented by the voltage and time dependencies of the conductances to individual ions although in their model also, the ion channels are either open or closed, the proportion of them open determining the instantaneous value of the conductance. Unfortunately Tasaki does not discuss the relationship between his ideas and those emerging from the use of 'patch' clamping of excitable membranes, presumably because the book was in press at the time the first accounts appeared (1980). Nevertheless this comment highlights the absence of all but a few references after 1977. Confessing to a personal interest, I was also slightly disappointed at the omission of any references to the considerable new literature on the topic of demyelination, yet another topic which Tasaki pioneered. However, notwithstanding these minor criticisms, this monograph, which spans almost 50 years of the highly original research carried out by this distinguished scientist, will be of particular interest to academic neurobiologists, both for the scholarly account of the subject of nervous excitability and for the challenge it contains particularly for young scientists 'not to complacently accept the majority view'.

T. A. SEARS

Progress in Clinical Neurophysiology. Volume 9. **Motor Unit Types, Recruitment and Plasticity in Health and Disease.** Edited by J. E. Desmedt. 1981. Pp. 416. Basel: Karger. Price DM 177.00.

This volume, the latest addition to Desmedt's series, is awkward to summarize because it contains reviews of a number of disparate topics. The term 'motor unit' in the title suggests a central unifying theme but, because motor unit activity constitutes most raw data from studies of the human motor system, that uniformity is more apparent than real. A few chapters do deal with the motor unit itself but most use EMG recordings to study other aspects of motor control. For this ninth volume, one assumes the authors were chosen rather than the topics—not necessarily a bad idea. However, such a selection method must make it difficult for an editor to find a credible intellectual framework for each volume including a new title which will honestly describe its contents.

The book begins with a review of the anatomy, histochemistry and mechanical twitch characteristics of single motor units. The first chapter, Kugelberg's inaugural lecture at the Sixth International EMG Congress in Stockholm in 1979, is a succinct and very useful review of the important studies in which he demonstrated that the normal muscle unit is metabolically and functionally a reflection of its motoneuron's discharge pattern and is not composed of several tightly packed groups of muscle fibres—significant milestones in the course of modern single motor unit analysis.

Next are several chapters devoted to Henneman's size principle for motoneuron recruitment in animals and man; they discuss data recorded under varying conditions such as ballistic *versus* ramp contractions. Henneman's principal of rank-ordering of motoneurons by size during recruitment is generally accepted; the most interesting research in this area now concerns mechanisms underlying this phenomenon. None of these newer studies is reviewed here.

Then come chapters whose titles promise discussion of locomotion, nerve and muscle disease, entrapment neuropathies and hemiplegia. Although at first glance such chapters would appear clinically relevant, they focus very narrowly upon somewhat esoteric aspects of single motor unit behaviour under these various circumstances; there is little to be learned here about these topics of obvious interest that has not been better covered in various textbooks of neuromuscular disease or clinical neurophysiology. For example, in the chapter on nerve and muscle disease, we are told yet once again that fibrillations occur with denervation, slowly progressive denervating diseases are often associated with large motor unit potentials and denervation potentials may be recorded from patients with myopathic diseases. The chapter which includes 'patients with entrapment neuropathies' in its title concludes there is no difference between these patients and normal subjects in the recruitment order of motor units following graded electrical stimulation (a most recondite study); it is hardly a chapter on clinical aspects of entrapment neuropathies.

From one of 3 chapters (28 per cent of the entire text) contributed by the Editor, in which he reviews 'Coherent Electromyography', the question arises, have electromyographers really been doing 'incoherent EMG' all these years? He defines 'coherent EMG' as ordinary EMG in which motor unit discharges trigger the oscilloscope sweep and a delay line is used so the entire motor unit action potential can be seen. This technique was an off-shoot of single fibre EMG and, as such, was developed and popularized by Stålberg who, in this chapter at least, is given little credit for his work. He and his colleagues in particular have been most productive in exploiting these and related EMG techniques in a clinical setting; practical material of that sort from a clinical electromyographer such as Stålberg would have provided at least some of what the Preface promised.

The Editor, in his preface says these '22 chapters have been designed to review most available data and current issues about motor units in health and disease'. He goes on to promise discussions of (1) 'mechanisms involved in different types of exercise training in sports medicine' and (2) 'an essential base for the analysis of motor performance in man in sports medicine, psychology, or physiology, and for electromyography in the diagnosis of motor disorders in clinical neurology'. Those are formidable goals, worthy of our best efforts for years to come, and if this volume is to be judged on the basis of whether it lives up to those promises, it certainly cannot be acknowledged a success. Most of these areas, such as exercise training, sports medicine, psychology and electromyography are mentioned very briefly indeed and readers primarily interested in one of them would find precious little here to satisfy an appetite whetted by the Preface. They will, however, agree with the Editor's statement that a 'single list of over 800 citations at the end of the book provides a comprehensive reference source about motor units'.

Given free rein, many of us are willing to write reviews of our earlier studies but, without an editorial nudge, each will not always write critically, cite others who have contributed significantly to the field or acknowledge the existence of contradictory published data. Such selective citation is particularly prominent in this volume. This lack of objectivity or fairness regarding the merits of other contributions (so important for good review articles) leads to considerable inhomogeneity with some chapters giving a balanced view and therefore being of much more interest to neurologists than others. Although all chapters, to the best of my knowledge, contain 'the truth', it cannot be said that all also contain 'the whole truth and nothing but the truth'.

Several chapters are very fine reviews of discrete topics (especially those by Kugelberg, Henneman and Robert Burke); although they are now several years old, I still find them instructive. In addition to these strong points, this volume has inadequacies typical of some nonrefereed publications. Speculation often exceeds data; there are no new data in most chapters. Although several present data which are otherwise unpublished, they tend to be insufficient to permit either the author or the reader to draw meaningful conclusions. Some chapters are timely as well as accurate and complete—others present a fragmented, incomplete or superficial view of their subject. Little attempt seems to have been made to integrate each chapter with the rest. In addition to his role as reader and compiler, the Editor might have urged a little less overlap and a bit more objectivity on some of his contributors.

For whom was this volume compiled and to what purpose? I found it interesting, am pleased to have it on my shelf and consult it frequently. It should also be interesting and useful, principally as a handy reference list, to neurologists, clinical neurophysiologists and others who are active investigators in these areas. It will not prove to be particularly valuable for clinicians or others interested in sports medicine, rehabilitation, electromyography or motor unit behaviour in health and disease.

ROBERT R. YOUNG

ANNOUNCEMENT

The Guarantors of *Brain* have recently established the Gordon Holmes Memorial Lecture to commemorate the outstanding contributions both to clinical neurology and to the basic neurological sciences made by Sir Gordon Holmes, a former Editor of *Brain*.

The first lecture will be delivered at 12 noon on Friday, November 4, 1983 in the Kennedy Lecture Theatre at the Institute of Child Health, Guilford Street, London, WC1, by Professor G. Baumgartner, University of Zürich. His title will be 'Present concepts of organization and function of the cerebral cortex'. Admission is free without ticket.

FORTHCOMING EVENTS

The Sixth International Symposium will be held from November 8 to 10, 1984 in Tokyo, Japan and focuses on topics of basic research, diagnosis and therapy in the area of brain oedema. Further information can be obtained from the Secretariat of the Sixth International Symposium on Brain Edema, Department of Neurosurgery, Tokyo Medical and Dental University School of Medicine, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113 Japan.

UCLA Extension and the UCLA Comprehensive Epilepsy Program will present 'An International Symposium on Basics Mechanisms of the Epilepsies', December

7–10, 1983, in San Diego, California. The symposium chairman is Dr Antonio V. Delgado-Escueto, Los Angeles, CA. The symposium is presented in conjunction with the National Institute of Neurological Diseases, Communicative Disorders and Stroke. Further information may be obtained from Ms Helen Nichunsky, UCLA Extension, Continuing Education in Health Science, PO Box 24901, Los Angeles, CA 90024. Tel. 213-825-7186.

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Brain

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VOLUME 106 · PART IV · DECEMBER 1983

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Notices of recent publications 1019

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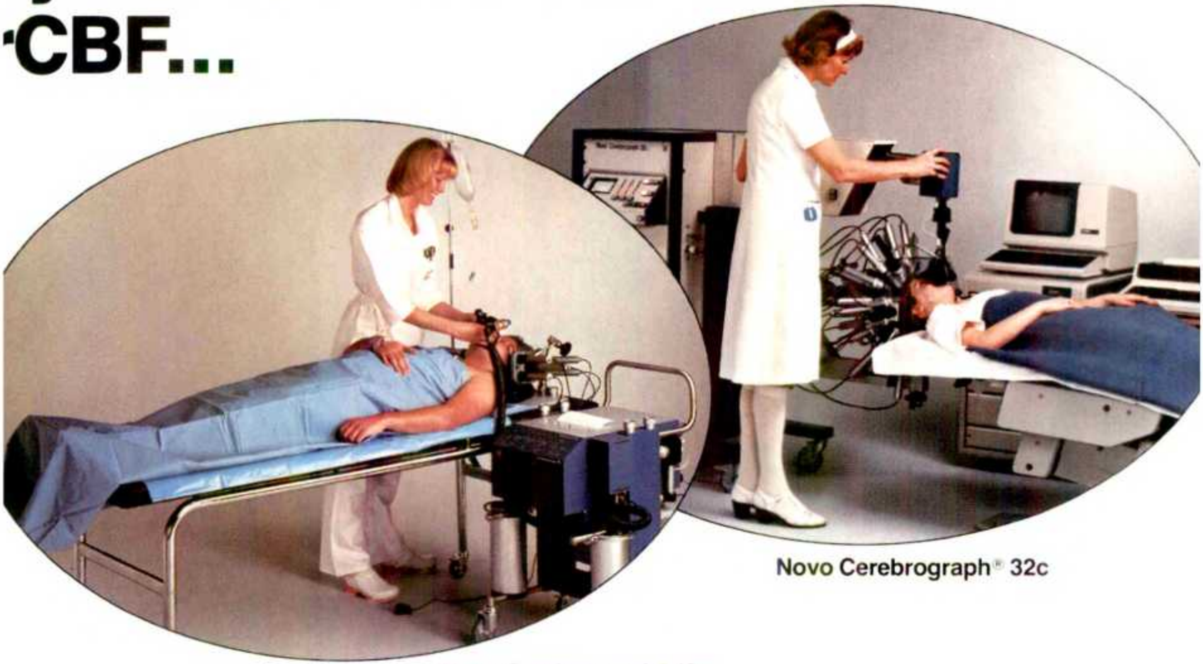

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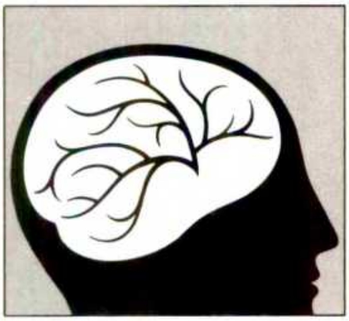

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PROGRESSIVE CENTRIPETAL DEGENERATION OF AXONS IN SMALL FIBRE DIABETIC POLYNEUROPATHY

A CLINICAL AND PATHOLOGICAL STUDY

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SUMMARY

A clinicopathological study is presented of 5 patients with a pseudosyringomyelic dissociation of sensory loss and severe autonomic disturbances related to diabetic polyneuropathy. Sensory loss which followed a pattern that suggested a length-related degeneration of fibres was associated with spontaneous pains in 3 patients. Plantar ulcers and neurogenic arthropathies were also present in 3 patients. The pathological changes in sural nerve biopsies included a severe loss of unmyelinated and small myelinated axons which appeared to be involved earlier than larger myelinated fibres. Distal degeneration of single fibres with subsequent axonal sprouting from the proximal axon was demonstrated in all patients. This severe axonal neuropathy was associated with primary and secondary segmental demyelination. Our observations are consistent with a progressive centripetal degeneration of axons in predominantly sensory diabetic polyneuropathy.

INTRODUCTION

Distal sensory polyneuropathy is the most common neurological complication of diabetes (Bruyn and Garland, 1970). In some patients pseudosyringomyelic dissociation of sensory loss, spontaneous pains and autonomic disturbances occur and suggest a predominant involvement of small myelinated and unmyelinated axons, as is observed in hereditary amyloid polyneuropathy (Andrade, 1952; Dyck and Lambert, 1969). We have investigated 5 diabetic patients in whom dissociated sensory loss followed a pattern consistent with a length-dependent degeneration of axons (Sabin *et al.*, 1978; Said, 1981) and have performed a qualitative and quantitative analysis of sural nerve specimens in an attempt to correlate signs and symptoms with the pathological observations.

CASE REPORTS

All patients included in this study had a polyneuropathy without other detectable explanation than diabetes.

Case 1

A 44-year-old woman had been found to be diabetic in 1968 and treated with oral hypoglycaemic agents. More recently treatment with insulin was begun but diabetic control remained poor and she experienced recurrent episodes of hypoglycaemia and of ketoacidosis. She started to complain of pains in the lower limbs in 1970 and developed urinary and faecal incontinence in 1976. Since 1972 she has experienced repeated episodes of feelings of coldness lasting 2 to 3 h. On examination, there were no abnormal motor signs. Severe sensory loss was present over the distal two-thirds of all four limbs, over the anterior and lateral aspects of the trunk up to the level of T2 dermatome, over the top of the scalp and in the perineal area. This predominantly involved pain and temperature sensibility. Light touch perception was impaired in a glove and stocking pattern. Vibration and position sense in the toes was preserved. The pattern of sensory loss was comparable to that illustrated in fig. 1. The patient was aware of loss of sensation only over the perineal area. The tendon reflexes were abolished in the lower limbs and decreased in the upper limbs. Autonomic disturbances included urinary and faecal incontinence and mild postural hypotension without tachycardia. The pupils were normal as were the other cranial nerves and the rest of the neurological examination.

The patient had diabetic retinopathy but no renal involvement. Motor nerve conduction velocity in the left peroneal nerve was 32 m s^{-1}, with a distal latency of 8.2 ms. The sural nerve sensory action potential was 2.2 μV (normal $>$ 10 μV). This case has been included in a previous study on length-dependent degeneration of axons (Said, 1981).

Case 2

A 26-year-old diabetic woman was referred because of painless burns of the hands with suspected syringomyelia. Diabetes had been discovered at the age of 13 years. Since then she has been treated with insulin with poor diabetic control and had had repeated episodes of ketoacidosis and hypoglycaemia. She had a retinopathy and proteinuria without renal insufficiency. She also had gangrene of the left second toe related to distal arteriopathy in the feet. She complained of feelings of coldness in the legs. Examination showed no abnormal motor signs. Pinprick and temperature sensation was lost over the distal two-thirds of the limbs and over the trunk up to T2 level. Only the midline and paramedian part of the posterior aspect of the trunk was spared. Loss of light touch sensibility was restricted to the feet and fingers. Joint position sense was preserved. Vibration sense was decreased in the feet but retained in the hands. The tendon reflexes were abolished in the lower limbs and decreased in the upper limbs. Several scars from painless burns were present in the hands. The patient complained of precipitate micturition. Motor conduction velocity in the left peroneal nerve was 36 m s^{-1} and 44 m s^{-1} in the left ulnar nerve. Sensory nerve action potentials could not be obtained from the sural nerves.

Case 3

A 58-year-old man had been found to be diabetic in 1963. He had been treated since then with oral hypoglycaemic agents until one year before admission when treatment with insulin was initiated. Good control of hyperglycaemia had never been achieved. The patient was referred because of burning pains in the feet in 1980. Scars of several painless burns were present. Motor examination disclosed a minimal (4/5) deficit of distal muscles in the lower limbs. Muscle strength was normal in the hands in spite of mild muscle wasting. Perception of temperature and pinprick sensation was abolished over the lower limbs up to a few centimetres below the groins, up to the middle third of the arms, over the anterior and lateral aspects of the trunk and over the top of the scalp. Light touch sensation was lost over a more restricted area in the limbs and was relatively intact over the trunk. Joint position and vibration sense was abolished in all four limbs. All tendon reflexes were lost except the triceps. There were neurogenic arthropathies of the left metatarsophalangeal joints. Autonomic disturbances included diarrhoea, postural hypotension (recumbent blood pressure 160/80 mm Hg, falling to 80/50 mm Hg after standing for 1 min, without tachycardia), sluggish pupils, impotence and excessive nocturnal sweating over the trunk. Motor conduction velocity was 44 m s^{-1} and the sensory action potential 3 μV (normal > 10 μV) in the median nerve. The patient had also a severe retinopathy and arterial insufficiency in the lower limbs.

Case 4

A 46-year-old woman had been treated for diabetes from 1973 to 1979 with oral hypoglycaemic agents, with poor control of hyperglycaemia. In 1979 a plantar ulcer developed over the metatarsal head of the left foot and a neurogenic arthropathy of the metatarsophalangeal joint of the fifth toe was noted. By that time she started to experience episodes of nocturnal diarrhoea and profuse sweating over the trunk and lower limbs. Treatment with insulin was begun in 1979. In 1980 motor examination showed only minimal distal weakness. Pain and temperature sensation was lost over the lower limbs up to the lower third of the thighs, over a glove distribution in the upper limbs and over the anterior trunk up to T2 level. Pinprick sensation was less affected than temperature over the trunk. Tactile sense was impaired over a glove and stocking pattern. Joint position and vibration sense was preserved. The ankle jerks were lost and the left knee jerk was decreased. Postural hypotension was noted (recumbent blood pressure 120/80 mm Hg, falling to 80/60 mm Hg after standing for 1 min, without a

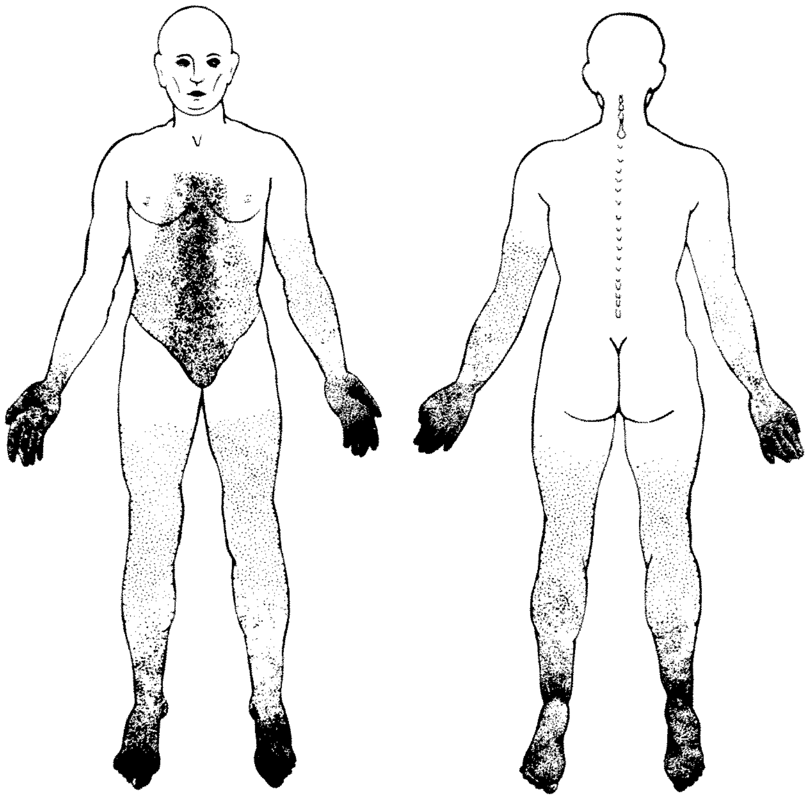

FIG. 1. Distribution of loss of temperature sensation in Case 5.

compensatory rise in pulse rate). The patient had diabetic retinopathy. Motor conduction velocity in the right peroneal nerve was 30 m s^{-1} with a distal latency at 4 ms. The right sural nerve action potential was 5 μV (normal $> 10\ \mu$V).

Case 5

A 26-year-old man had been treated with insulin since 1964. He was referred in 1979 for neurogenic arthropathy of the left ankle joint and plantar ulcers. Good diabetic control had never been achieved. Episodes of hypoglycaemia and ketoacidosis were frequent. He had diabetic retinopathy.

Motor examination showed no abnormality. There was a painless ulcer over the metatarsal heads of the right foot. Temperature sense was lost up to the upper third of the thighs, up to elbow level in the arms and over the anterior trunk up to T2 level (fig. 1). Loss of pinprick sensation was of the same pattern but over a slightly more restricted area. Light touch sense was lost over a glove and stocking distribution. Perception of vibration was decreased over the toes, but joint position sense was preserved. The ankle jerks were abolished. Autonomic disturbances included Argyll Robertson pupils, nocturnal diarrhoea, retrograde ejaculation and postural hypotension (recumbent blood pressure 130/80 mm Hg, falling to 100/70 mm Hg after 1 min in the upright position, without rise in pulse rate). Motor conduction velocity of the peroneal nerve was at 35 m s^{-1}. Sensory action potentials could not be obtained from the sural nerves.

METHODS

A fascicular biopsy of the sural nerve was performed under local anaesthesia at the ankle level in each patient. One to three fascicles were removed and fixed in 3.6 per cent glutaraldehyde in 0.1. phosphate buffer at pH 7.4 and iso-osmolality. After dehydration in ethanol, the specimens were embedded in Epon. Transverse sections 1 μm thick were stained with 1 per cent thionin. The density per mm^2 of endoneurial area and the diameter of myelinated fibres were determined using a × 100 objective under oil and an automated system (Quantimet, Cambridge Instruments and a PDP 1134 computer) under the control of the operator (Selva *et al.*, 1981). Control observations were made on sural nerve specimens from 2 adult patients aged between 30 and 40 years. Another nerve fascicle was osmicated after fixation, rinsed in buffer and put in 66 per cent glycerol. One hundred consecutive fibres were dissected in pure glycerol under the microscope and categorized according to their morphological changes (Dyck, 1975). Internodal lengths of single fibres of different sizes were measured with a micrometer (Fullerton *et al.*, 1965). The internodal lengths were plotted against the average diameter of the widest internode. A specimen from a 30-year-old man without detectable neurological disease was used as normal control.

Thin sections were prepared using an LKB Ultrotome III, stained with uranyl acetate and lead citrate, and examined in an electron microscope (Siemens Elmiskop CT 150). Counts of unmyelinated

TABLE. RESULTS OF TEASED FIBRE STUDIES IN CASES 1–5

Case	*Normal* (%)	*Segmental demyelination and/or remyelination* (%)	*Axonal degeneration* (%)
1	47	36	17
2	78	16	6
3	55	26	19
4	30	46	24
5	72	24	4

fibres were made on photographs at a final magnification of × 20000. Approximately three-quarters of the embedded fascicles were counted. The unmyelinated fibres were differentiated from Schwann cell subunits by their lighter appearance, round shape, lack of rough endoplasmic reticulum, higher density of microtubules and by the presence of a mesaxon.

RESULTS

Single Fibre Studies

These results are summarized in the Table. The incidence of fibres showing myelin changes characteristic of the different stages of wallerian type varied from 6 per cent in Case 2 to 24 per cent in Case 4. Abnormalities of myelination, which included

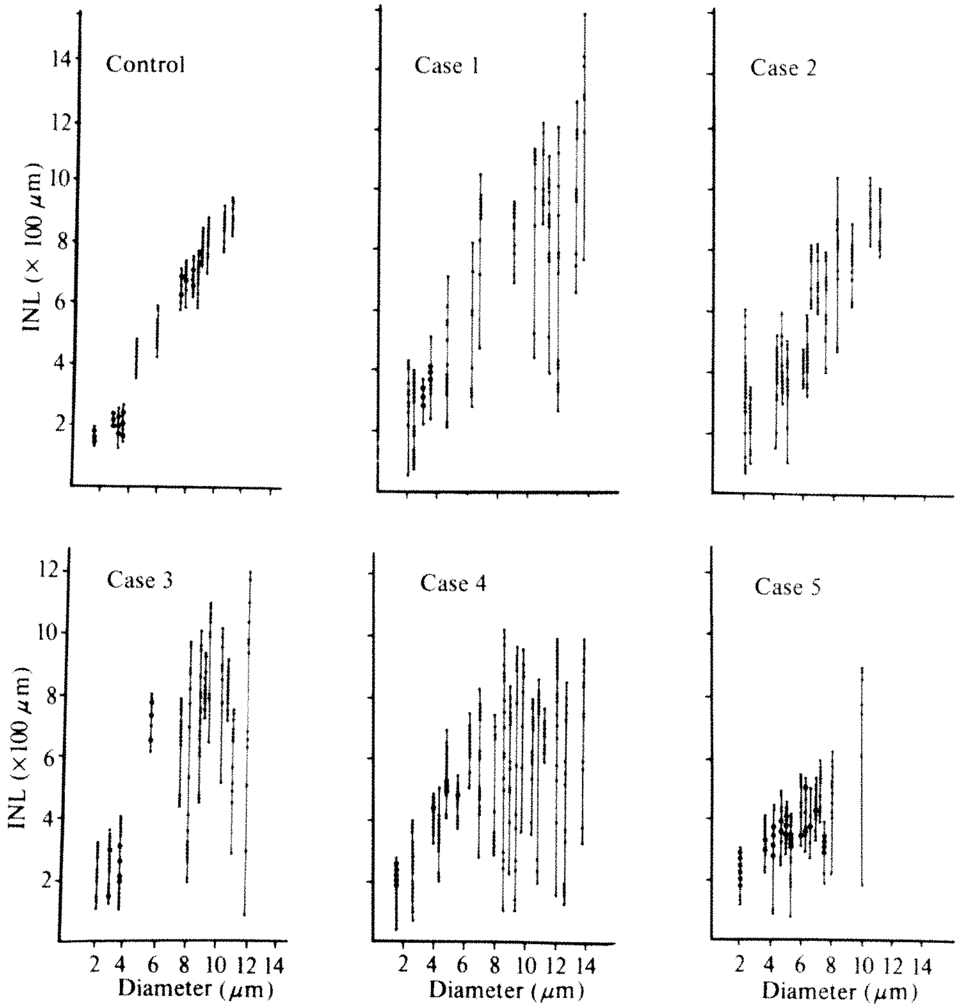

FIG. 2. Relationship between internodal length (INL) and fibre diameter in sural nerve. For each fibre the average diameter of the widest internode has been plotted against the length of the internodes. Small dots represent one internode and large dots 5 internodes of comparable length.

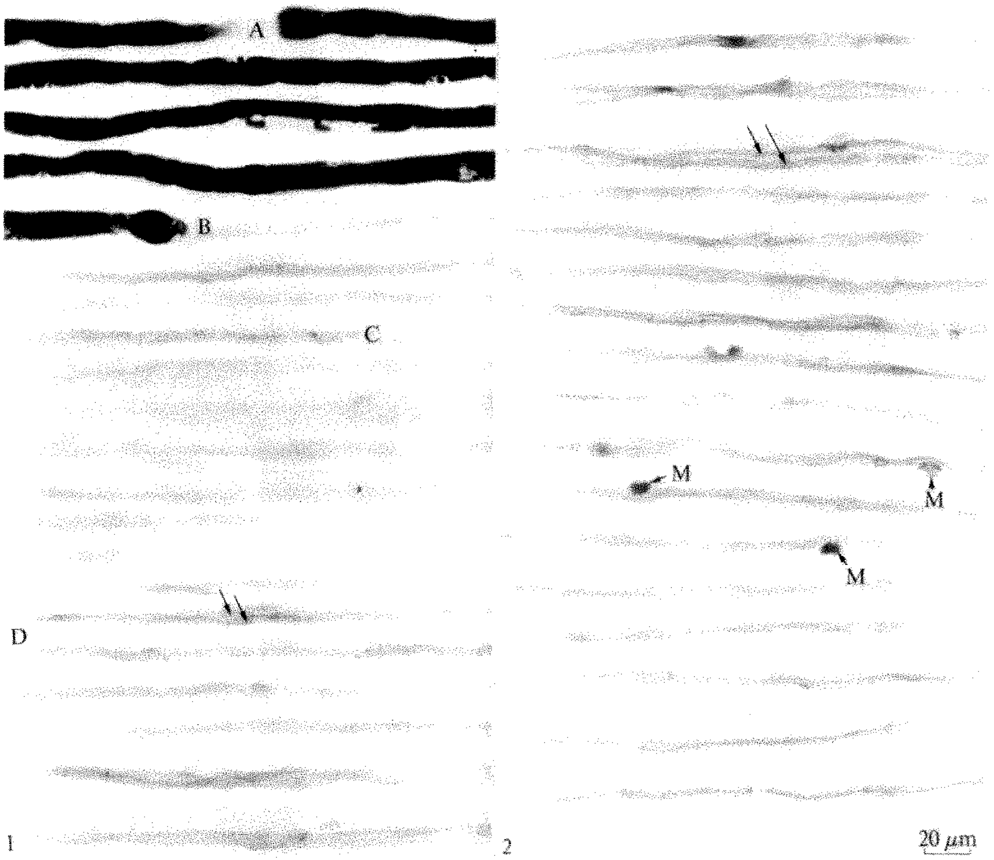

FIG. 3. *Case 3.* Consecutive segments of a regenerating fibre isolated after osmication. The proximal end is at the top left of the left hand panel (1), the distal end at the bottom right of the right hand panel (2). From top left to A is the original myelin sheath. At A, paranodal demyelination of the most distal node of Ranvier of the original fibre is seen. Axonal regeneration starts at B. A new myelin sheath is present between B and C. From C to D a myelin sheath is hardly visible. Distal to D, two regenerating fibres are present (arrows). Myelin debris (M) from the original fibre is still visible. These findings characterize axonal regeneration by sprouting of the proximal axon after degeneration of its distal part.

paranodal and segmental demyelination and short remyelinated internodes, ranged from 16 per cent of the fibres in Case 2 to 46 per cent in Case 4. The internodal length measurements are given in fig. 2. Variations in internodal length characteristic of a remyelinating process were prominent in Cases 1, 3, 4 and 5. In the specimens from all 5 patients, fibres were isolated which showed changes characteristic of regeneration. Proximal to a node of Ranvier, the preserved portion of the fibre was of larger diameter and had a thicker myelin sheath, more densely stained by osmium tetroxide, than in the regenerated region (fig. 3). Internodal length in the regenerating portion of the fibres was shorter (Vizoso and Young, 1948). Branching of the regenerating fibre was observed at one or several nodes distal to its origin from the proximal axon (fig. 3). The node proximal to the junction of original and regenerated portions of the isolated fibre was widened; in some fibres an intercalated internode related to remyelination of such paranodal demyelination had taken place. In some fibres paranodal demyelination of several consecutive nodes of the original fibre was present proximal to the origin of the regenerating axon. The regenerating axons were not uniformly myelinated. In some fibres, proximal segments of sprouts were not myelinated while more distal portions were already thinly myelinated. The size of some regenerating fibres decreased distally. In others large deposits of myelin debris resulting from degeneration of the distal part of the original fibre were still present in the band of Büngner in which axons were sprouting (fig. 3). Focal accumulations of faintly osmicated Schwann cell nuclei were encountered in regenerating fibres (fig. 4) and associated with an enlarged cuff of Schwann cells.

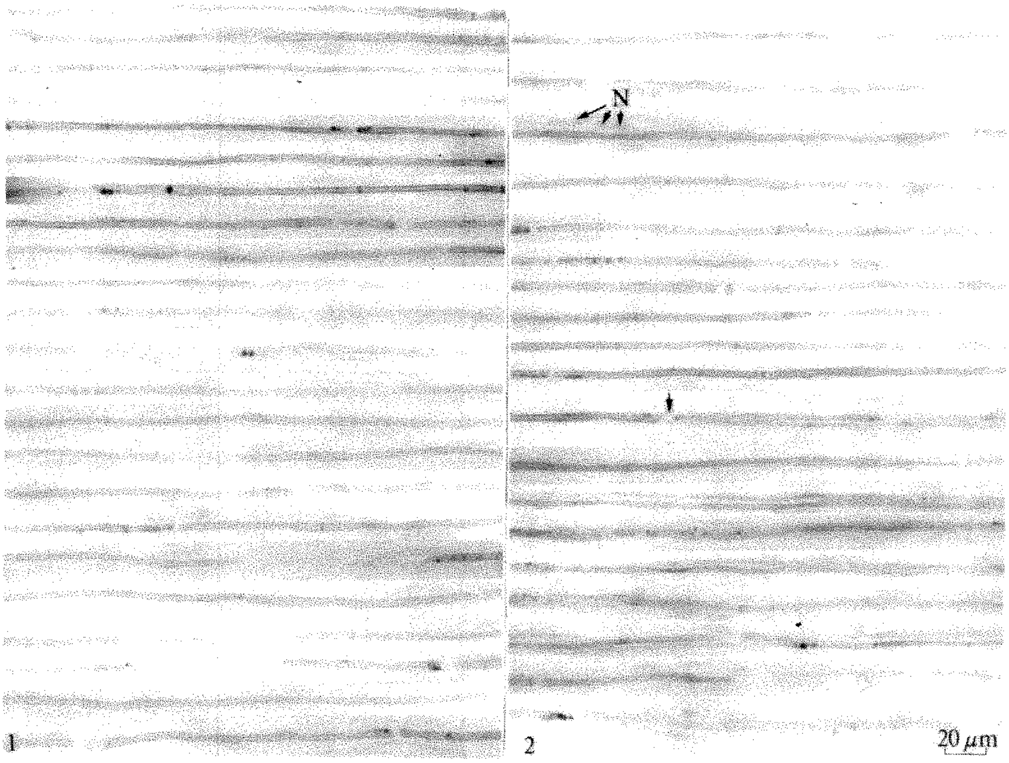

FIG. 4. *Case 4.* Consecutive segments of a regenerating isolated fibre after osmication. The proximal end is at the top left of the left hand panel of (1) and the distal end at the bottom right of the right hand panel of (2). Several internodes are not completely myelinated. Note the conspicuous variation in internodal length. There is a focal accumulation of Schwann cell nuclei (N), faintly stained by osmium tetroxide and an enlargement of the cuff of Schwann cells surrounding the myelin sheath. Two smaller fibres arise from the node indicated by the arrow.

Myelinated Fibre Morphometry

The density of myelinated fibres (per mm^2 endoneurial area) was 3200, 2500, 1300, 820 and 1260 in Cases 1-5, respectively (fig. 5). The smaller fibres were selectively involved in Case 1, in whom the density of larger fibres was comparable to control values. In Case 2, small fibre axonal loss predominated but the number of larger fibres was also slightly decreased. In Cases 3 and 4, fibres of all diameters were affected. In Case 5, only fibres smaller than 8 μm were present. Most were in clusters of 2 to 5, surrounded by a ring of Schwann cell processes (fig. 6). Such clusters of regenerating fibres were present in all specimens.

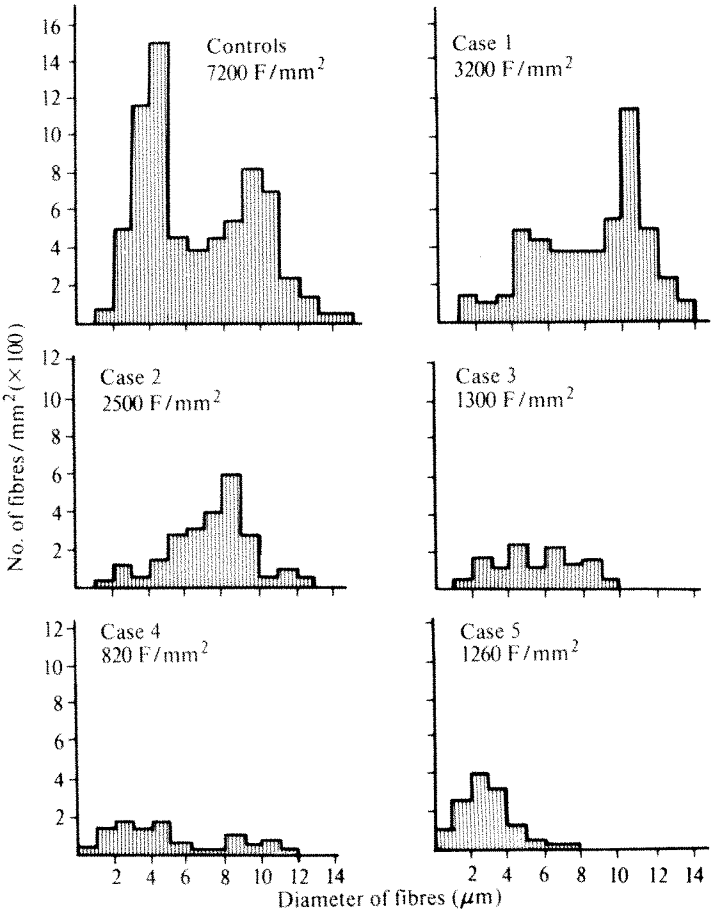

FIG. 5. Size-frequency histograms for myelinated fibres in sural nerve.

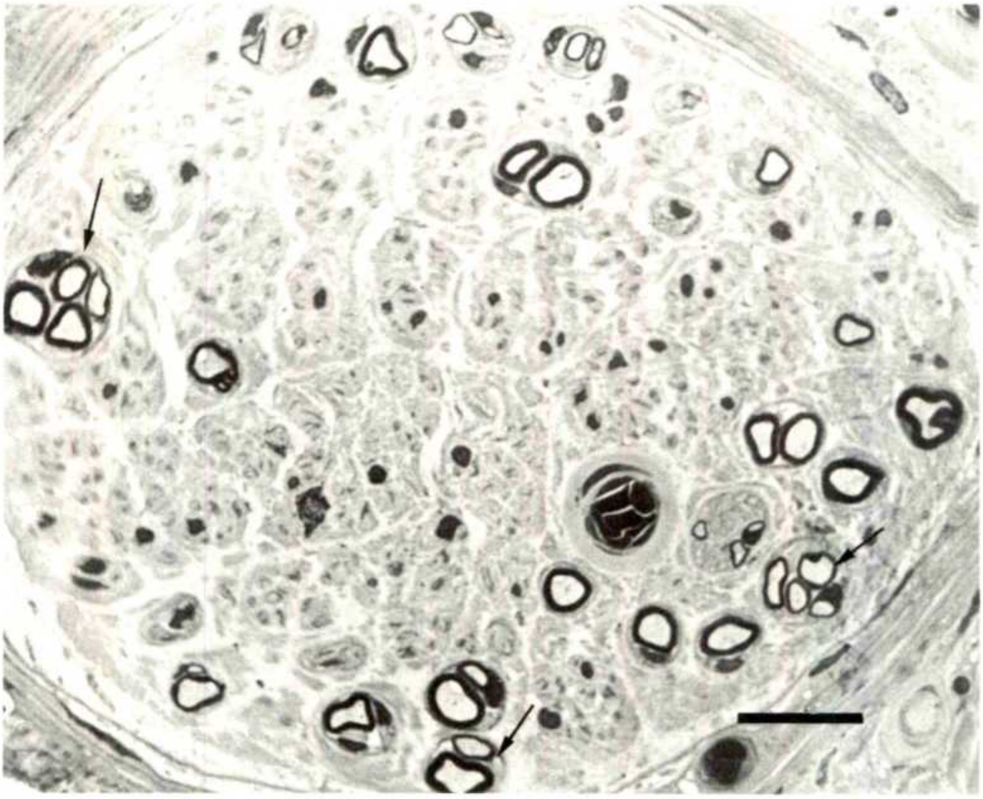

FIG. 6. Semithin sections of sural nerve from *Case 5*. Thionin stain. There is a conspicuous reduction in the density of the myelinated fibres. Most of these are surrounded by a ring of Schwann cell processes. Several clusters of regenerating fibres are present (arrows).

Electron Microscopy

The density of myelinated and unmyelinated axons was markedly reduced in all patients. The myelinated fibres showed evidence of demyelination, degeneration and regeneration (figs. 7 and 8). Many Schwann cell processes were flattened. Tiny Schwann cell subunits were surrounded by a loose basal lamina which was often duplicated. At times only the basal lamina could be seen. Some bands of Büngner derived from the degeneration of myelinated nerve fibres contained myelin debris and were associated with regenerating axon sprouts. In some clusters of regenerating fibres surrounded by a common basement membrane, only the larger axonal sprouts were myelinated (fig. 8). Myelinated fibres surrounded by additional rings of Schwann cell processes were common in Cases 2 and 5. These formations, which often contained several axons, imitate 'onion bulb' hypertrophy but are actually regenerating axons of the type observed in the isolated fibre preparations.

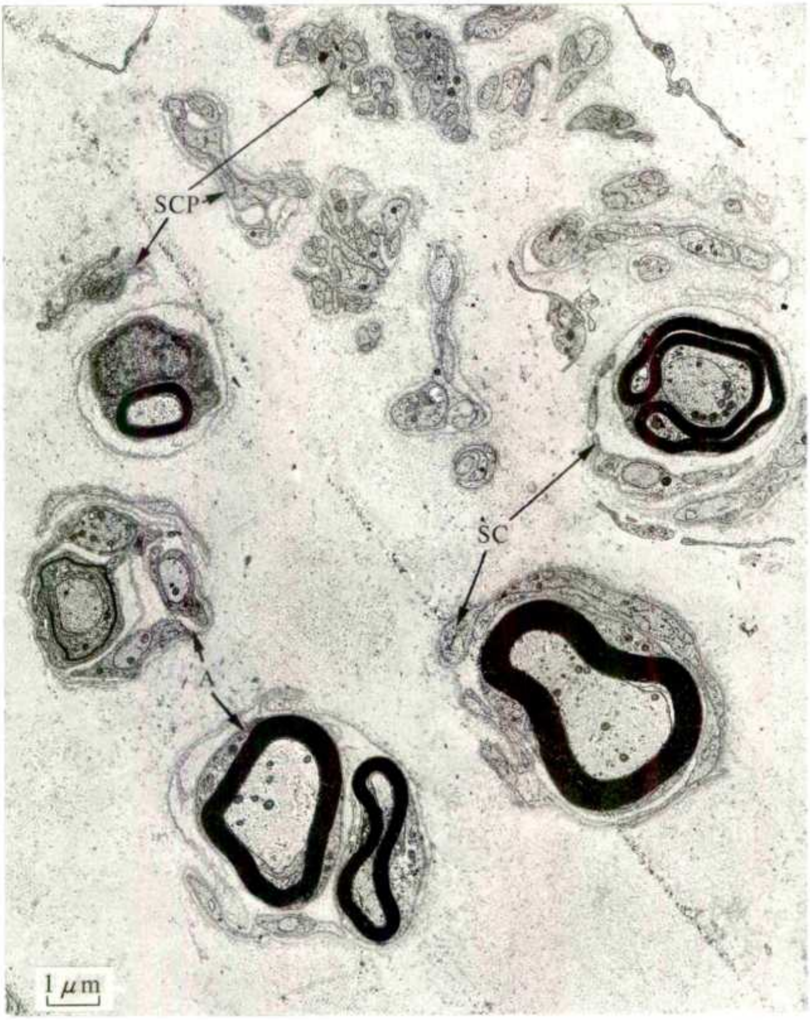

FIG. 7. Electron micrograph of sural nerve from *Case 2*. The myelinated fibres are surrounded by Schwann cell processes (SC). Two clusters of regenerating axons (A) are present (*see* fig. 8 for detail). The myelin sheath of the fibre on the right (arrow) has an unusual shape which probably represents a section through a loop of myelin near a node of Ranvier. Many Schwann cell subunits (SCP) are devoid of axons.

The density of unmyelinated axons was conspicuously reduced in all cases in comparison with the normal range of 19000 to 65000/mm^2 (*see* review by Ochoa, 1978). The values (per mm^2 endoneurial area) were 2025, 660, 1350, 1160 and 6000 in Cases 1-5 respectively. Flattened denervated Schwann cell processes characteristic of degeneration of unmyelinated axons (Ochoa, 1978) were common (fig. 9). Groups of miniature regenerating unmyelinated axons were observed (fig. 10). The difficulty in differentiating small unmyelinated axons with certainty from some Schwann cell processes may induce a bias

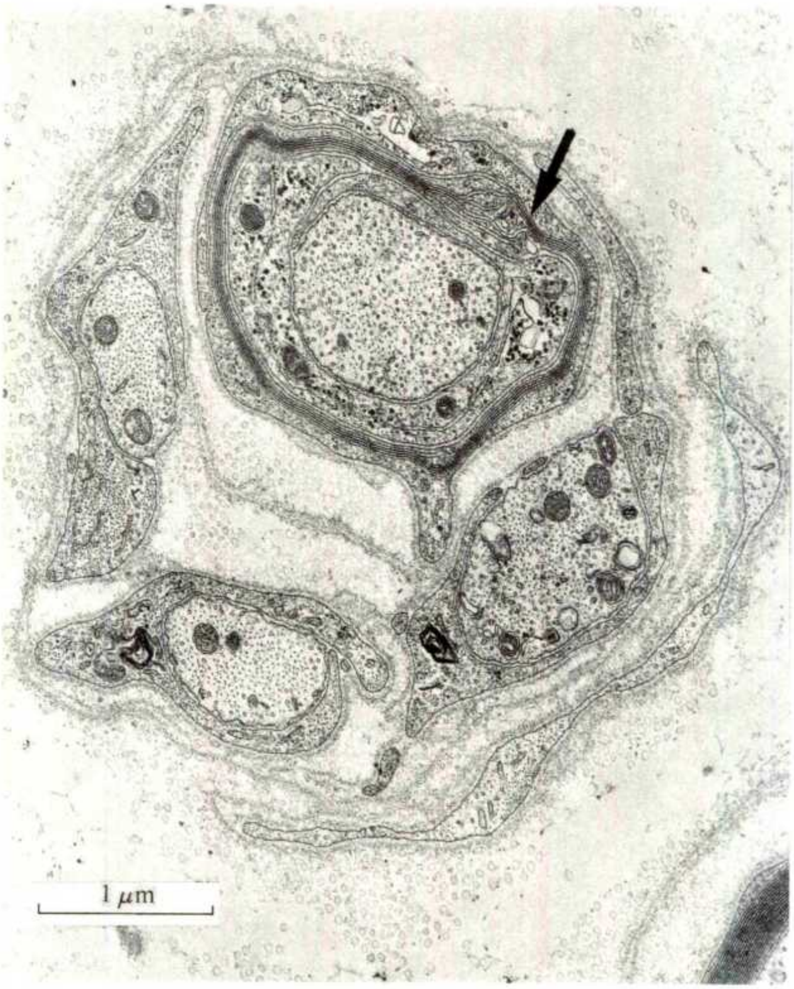

FIG. 8. Electron micrograph of sural nerve from *Case 2* (detail from fig. 5). Four axonal sprouts are clustered and surrounded by a common basement membrane which is duplicated in places. Only one of these regenerating axons possesses a myelin sheath (arrow).

in favour of unmyelinated axons, but their total density was so dramatically reduced in our patients that this would not have greatly modified the magnitude of axonal loss.

DISCUSSION

Our 5 patients presented with severe sensory and autonomic disturbances due to diabetic polyneuropathy. The pseudosyringomyelic dissociation of sensory loss accounts for the painless burns with which the neuropathy presented in Cases 2

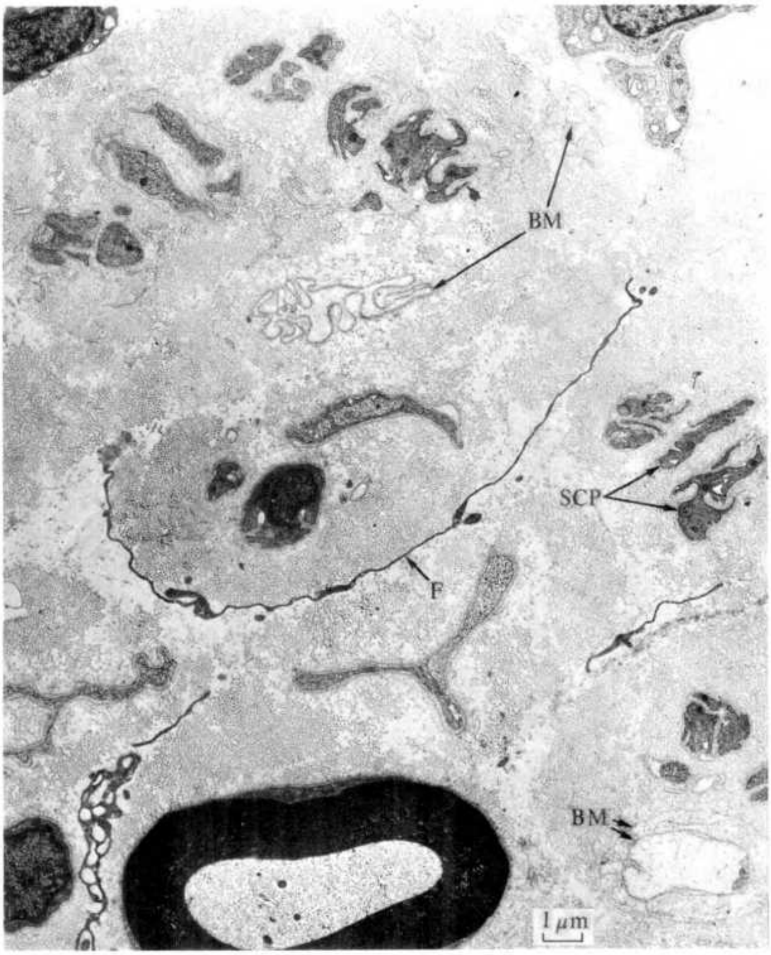

FIG. 9. Electron micrograph from *Case 3* showing a severe decrease in density of unmyelinated axons. Most of the Schwann cell subunits (SCP) are flattened and devoid of axons. BM = basement membrane, F = fibroblast process.

and 3. The proximodistal gradient of sensory loss was consistent with a length-dependent degeneration of fibres involving first the longest fibres of the lower limbs, then progressing to the upper limbs when axons of shorter length were affected. Sensation was lost over the anterior trunk when the intercostal nerves were affected distally, and the top of the scalp after involvement of the longest fibres of the trigeminal nerve (Sabin *et al.*, 1978). A comparable proximodistal gradient of sensory loss has been observed in severe axonal polyneuropathies of different origin, namely, diabetes, familial amyloidosis (Sabin *et al.*, 1978) and chronic alcoholic intoxication (Said, 1981).

Three of the 5 patients had lower limb neurogenic arthropathies which in 2 were

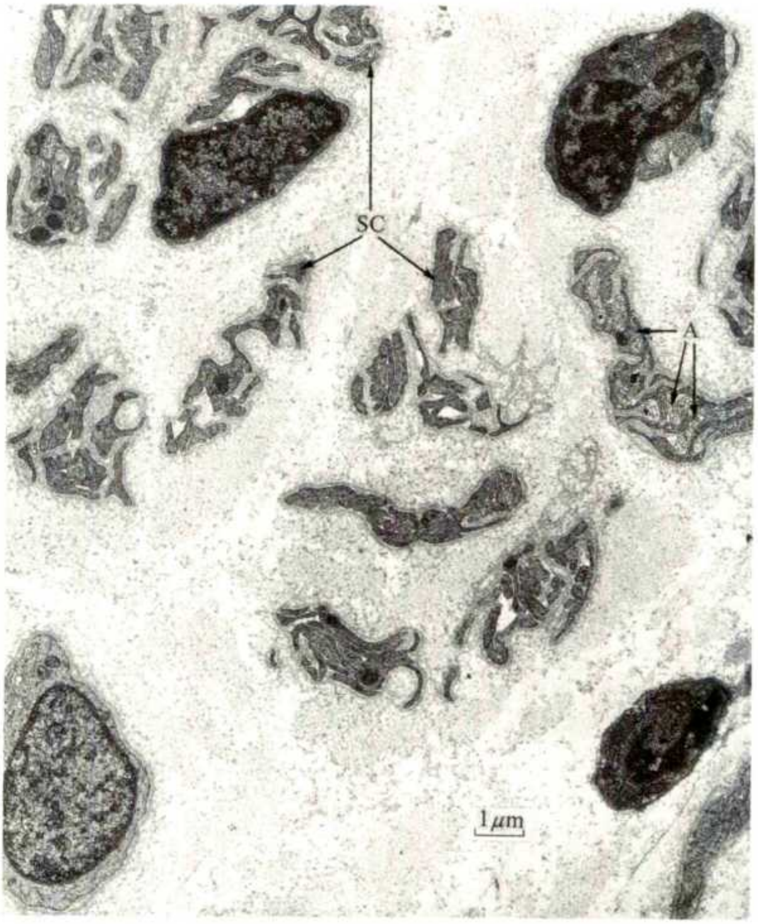

FIG. 10. Electron micrograph from *Case 1* showing Schwann cell processes devoid of axons (SC). On the right, regenerating unmyelinated sprouts (A) have a lighter appearance than the Schwann cell processes.

associated with plantar ulcers. Trophic changes of this kind, which are common in diabetic polyneuropathy (Martin, 1953), are known to complicate neuropathies of different origin (Spillane and Wells, 1969) when loss of pain sensation is associated with minimal motor deficit allowing walking to continue and painless trauma to occur. Diabetic microangiopathy does not seem to play an important role in the onset of such changes which are likely to be the consequence of minor trauma to insensitive plantar soles, bones and joints (Leplat, 1855; Sabin and Swift, 1975; Thomas and Eliasson, 1975; Said, 1980) and should accordingly be prevented.

In a recent study on acrodystrophic neuropathies of different origin, mainly alcoholic (Said, 1980), axonal loss was a constant finding but did not predominantly affect unmyelinated axons, as it did in the patients of this series.

Signs and symptoms of diabetic dysautonomia, namely, postural hypotension without a compensatory rise in pulse rate, reduced pupillary responses to light and Argyll Robertson pupils, nocturnal diarrhoea, genitourinary dysfunction, faecal incontinence, profuse sweating over the trunk and feelings of coldness (Rundles, 1945; Low *et al.*, 1975) were present in our patients. A proximodistal gradient of autonomic abnormalities has also been suggested (Waxman, 1980) and it is likely that the conspicuous loss of unmyelinated axons found in sural nerve specimens in the present study was common to sensory and autonomic nerves.

In a study on painful diabetic polyneuropathy, a reduction in density of myelinated fibres predominating in small fibres and an excess of small regenerating unmyelinated fibres contrasting with a mild decrease in the density of larger unmyelinated fibres have been observed (Brown *et al.*, 1976). Our cases were obviously more severe and spontaneous pain was present only in 3, but we did not find a marked difference in the density of unmyelinated axons between patients complaining of spontaneous pain and those who did not. Sprouting of unmyelinated axons occurred but was notably insufficient to compensate the loss observed in the biopsies. It is possible, however, that the incidence of regenerating unmyelinated fibres was higher in proximal parts of the nerves.

Dissociated sensory loss and severe autonomic disturbances suggest that small myelinated and unmyelinated fibres are predominantly involved (*see* review by McIntyre, 1980). Case 1, whose sural nerve retained the highest density of fibres, had a selective loss of small myelinated fibres. In Case 2, loss of small myelinated fibres was obvious and was associated with a slight reduction in density of the larger fibres. In Cases 3 and 4, all sizes of fibres were severely affected. In Case 5, only small myelinated fibres were present and they were likely to represent sprouts from larger axons, because most were clustered and surrounded by a ring of flattened Schwann cell processes with a pseudohypertrophic appearance (Bischoff, 1969; Vital *et al.*, 1973), as seen in regeneration. Such small axons possibly retain the functions of larger fibres. These observations demonstrate that the question of the predominance of involvement of myelinated fibre subpopulations cannot easily be assessed through fibre histograms, as has been stressed by others (Ochoa, 1970). A careful clinical examination may be more informative in this respect.

Isolated nerve fibre studies showed a varying incidence of demyelination, remyelination and axonal degeneration (Thomas and Lascelles, 1966; Chopra *et al.*, 1969). The question as to whether segmental demyelination in diabetes is a primary demyelination or a phenomenon secondary to axonal involvement is still controversial (Thomas and Eliasson, 1975). In the present study, the incidence of demyelinated fibres is much higher than that observed in common axonal neuropathies in man, for example, in subacute or chronic forms of alcoholic neuropathy (Said, 1980). This observation is in favour of a primary demyelination of fibres in relation to disturbances of Schwann cell functions by the metabolic abnormalities related to diabetes. Segmental demyelination is likely to be secondary to axonal involvement when wide paranodal demyelination affects one or several consecutive nodes of Ranvier proximal to the site of axonal breakdown, as seen in this study and in experimental wallerian degeneration (Lubińska, 1959). Clustering of demyelinated internodes on single fibres also suggests a process related to minor axonal involvement as it occurs in some patterns of uraemic polyneuropathy (Dyck *et al.*, 1971; Thomas *et al.*, 1971; Said *et al.*, 1982*a*). Abnormalities of myelination of regenerating fibres were common. We conclude from our observations that both primary and secondary segmental demyelination occur in diabetic polyneuropathy.

Regenerating isolated fibres have been identified in diabetes by the presence of short internodal segments contrasting with thick diameter (Behse *et al.*, 1977), following criteria established in experimental conditions (Vizoso and Young, 1948). In human neuropathies, however, as axonal lesions and segmental demyelination are often associated, such criteria do not appear reliable to us. The reason is that remyelinated internodes after segmental demyelination can only be differentiated from those that have myelinated after sprouting when the original myelin sheath has been reached by dissection on both sides of the remyelinated area. In consequence, our criteria for identifying regeneration in isolated fibres are the following. (1) The identification of the site of transition between the original fibre and the regenerated region, provided that division of the regenerating axon is clearly seen, or large deposits of myelinated debris from the original myelin sheath are still in contact with the regenerating fibre. When it follows segmental demyelination, remyelination occurs only when myelin debris has already been removed (Hall and Gregson, 1978). (2) Division of a small myelinated fibre into two or more smaller fibres is also sufficient to identify single regenerating fibres in sural nerve specimens, especially if associated with the presence of myelin debris. We have also observed similar regenerating fibres in sensorimotor diabetic polyneuropathy and in other conditions including uraemia (Said *et al.*, 1982*a*) and amyloidosis (Said *et al.*, 1982*b*).

We conclude from our pathological observations that distal degeneration of axons followed by axonal sprouting is an important feature of diabetic polyneuropathy. In the small fibre type of diabetic neuropathy, the unmyelinated and small myelinated fibres are involved before large myelinated fibres. Primary and secondary segmental demyelination are also a frequent finding. The neuropathy seems to progress centripetally by the involvement of longer lengths of axon associated with abortive axonal regeneration.

The cause of diabetic neuropathy is not known and the reason why unmyelinated and small myelinated fibres are selectively affected in some patients is also not understood. A differential susceptibility of these fibres to variations of endoneurial fluid composition might be considered; it is noteworthy that in all our patients, control of hyperglycaemia was poor. When axons are so dramatically affected, as in the present cases, only good long-term control of hyperglycaemia is likely to induce a significant improvement of the neuropathy by allowing efficient axonal regeneration.

ACKNOWLEDGEMENTS

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THE PREDICTIVE VALUE OF CEREBROSPINAL FLUID ELECTROPHORESIS IN 'POSSIBLE' MULTIPLE SCLEROSIS

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SUMMARY

We undertook a prospective study of 183 patients with monosymptomatic demyelination to determine the predictive value of the finding of cerebrospinal oligoclonal banding (OB) for the subsequent development of clinically definite multiple sclerosis. The results of this study indicate that patients with monosymptomatic demyelination who are OB positive are at significantly higher risk than those who are OB negative to develop clinically disseminated disease over the period of follow-up in this study. Positive OB is associated with a higher frequency of electrophysiological abnormalities than negative OB, suggesting that OB development correlates with the degree of biological dissemination. The observation that some patients develop OB during the course of the disease has practical implications for the follow-up of patients with unifocal disease and negative banding.

INTRODUCTION

The presence of oligoclonal IgG banding on CSF electrophoresis is well established in patients with clinically definite multiple sclerosis (CDMS) (Laterre *et al.*, 1970; Link and Müller, 1971; Vandvik and Skrede, 1973; Olsson and Pettersson, 1976; Thompson, 1977; Ebers and Paty, 1980). However, the demonstration of oligoclonal banding is of less value in patients with CDMS than in the common clinical situation in which the diagnosis is not possible on clinical grounds or is in doubt. We undertook a prospective study of patients with monosymptomatic demyelination to determine the predictive value of the finding of CSF oligoclonal banding for the subsequent development of CDMS.

MATERIALS AND METHODS

We reviewed 250 patients who were seen at University Hospital, London, Ontario between 1974 and 1982. On the basis of history and neurological examination all these consecutive patients were initially considered to have 'possible' multiple sclerosis which included Rose's possible and probable categories (Rose *et al.*, 1976). However, we restricted this study to those patients with *objective* evidence of white matter disease who had clinically unifocal disease (most commonly optic nerve, brainstem or spinal

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cord involvement). Sixty-seven patients did not fulfil the above criteria or could not be followed adequately and were therefore excluded (Table 1).

CSF was obtained at the initial diagnostic assessment in most cases and evaluated for the presence of oligoclonal banding as previously described (Ebers and Paty, 1980). Evoked potential studies were performed on the majority of patients to look for evidence of subclinical dissemination of disease detectable by electrophysiological methods. These studies consisted of auditory evoked responses (Ebers *et al.*, 1981), visual evoked responses (Blume *et al.*, 1977), and blink reflexes (Yates and Brown, 1981) and the results were considered abnormal only if they were beyond three standard deviations from the mean.

TABLE 1. PATIENTS WITH 'POSSIBLE' MULTIPLE SCLEROSIS EXCLUDED FROM STUDY

CDMS* from onset	25
Lost to adequate follow-up	23
Another diagnosis determined in follow-up	9
Absence of objective disease	6
Died	4
Total	67

* Clinically definite multiple sclerosis.

Oligoclonal IgG banding (OB) had been found in 83 of the 183 patients in the study followed for a mean period of 34.1 months. It was absent in 100 patients followed for a mean period of 33.9 months. We strictly adhered to the criteria set forth by Schumacher *et al.* (1965) in defining those patients who eventually went on to develop CDMS. We did, however, include two patients in the OB+ group and one patient in the OB− group who we felt had progressed to CDMS because they had developed bilateral and sequential optic neuritis. Although the nosological position of recurrent optic neuritis is in doubt, our own view is that a second episode of optic neuritis in the other eye fulfils the criteria for the disease. This view is supported by the work of Compston *et al.* (1978) who found that recurrent optic neuritis was a highly significant risk factor for the subsequent development of CDMS. 'Isolated' optic neuritis still is not a clinical-pathological entity separate from multiple sclerosis.

RESULTS

To investigate the possibility that OB discriminates between two clinically distinct groups of patients, the clinical features in OB+ and OB− patients were compared. The OB+ and OB− patients were divided according to their major sites of anatomical involvement as seen in fig. 1A, B and were found to be quite similar. The two groups were also similar in terms of mean age of onset (36.3 yrs *vs* 37.5 yrs, respectively) although the OB+ group had a slightly higher female:male ratio (2.2 *vs* 1.8, *see* fig. 2A, B). Duration of disease denoted the time from the onset of the first symptom until the last evaluation in the multiple sclerosis clinic. This differs from the period of follow-up which is the time from initial CSF analysis to the last clinical evaluation. The rather lengthy mean duration of disease reflects the inclusion of chronic myelopathies often seen after relatively long duration of symptoms. Nevertheless, the OB+ patients had a longer mean duration of disease than the

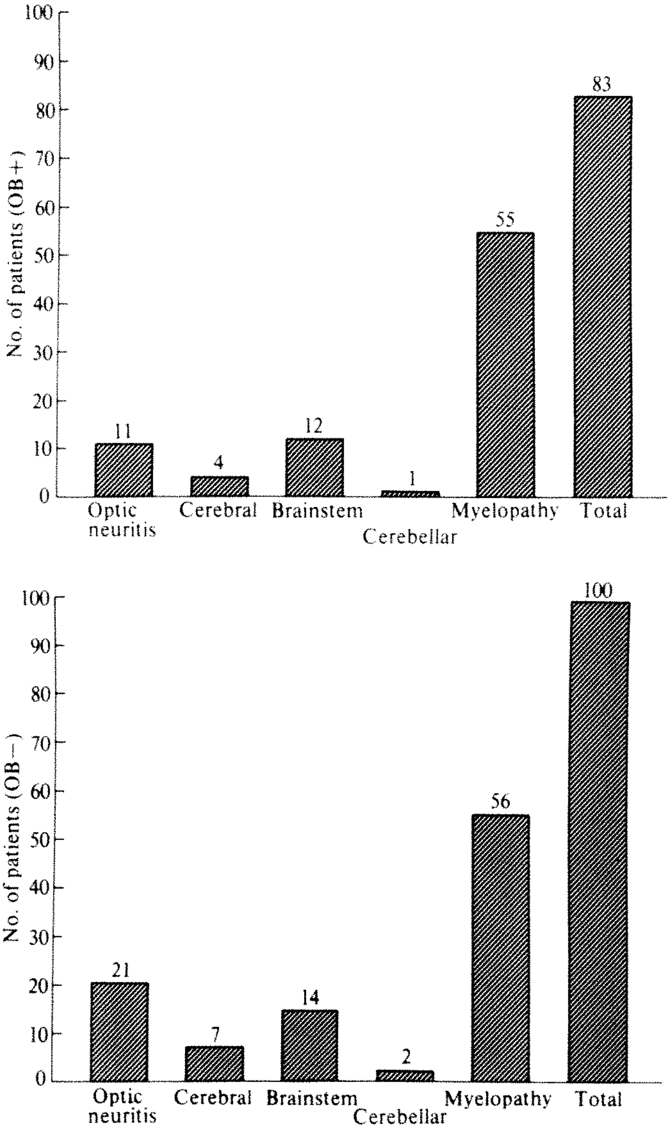

FIG. 1A. Major sites of anatomical involvement in 83 patients with 'possible' multiple sclerosis and oligoclonal banding in CSF (OB+). Results for 83 patients with a mean follow-up period of 34.1 months. B, major sites of anatomical involvement in 100 patients with 'possible' multiple sclerosis without oligoclonal banding in CSF (OB−). Results for 100 patients with a mean follow-up period of 33.9 months.

OB− patients (7 yr 8 m *vs* 5 yr 6 m) and only 16/83 patients in the former group compared with 40/100 in the latter group had a duration of illness of less than two years ($P < 0.005$, $\chi^2 = 9.17$) (*see* fig. 3A, B). Furthermore, since the period of follow-up was very similar in the OB+ and OB− groups (34.1 months *vs* 33.9 months), the OB+ patients had a longer duration of disease at the time of initial assessment.

The frequencies with which CDMS developed in the follow-up period for the OB+ and OB− groups are shown in Table 2. Of 83 patients with OB (mean follow-up of 34.1 months), 20 patients or 24 per cent developed clinically definite multiple

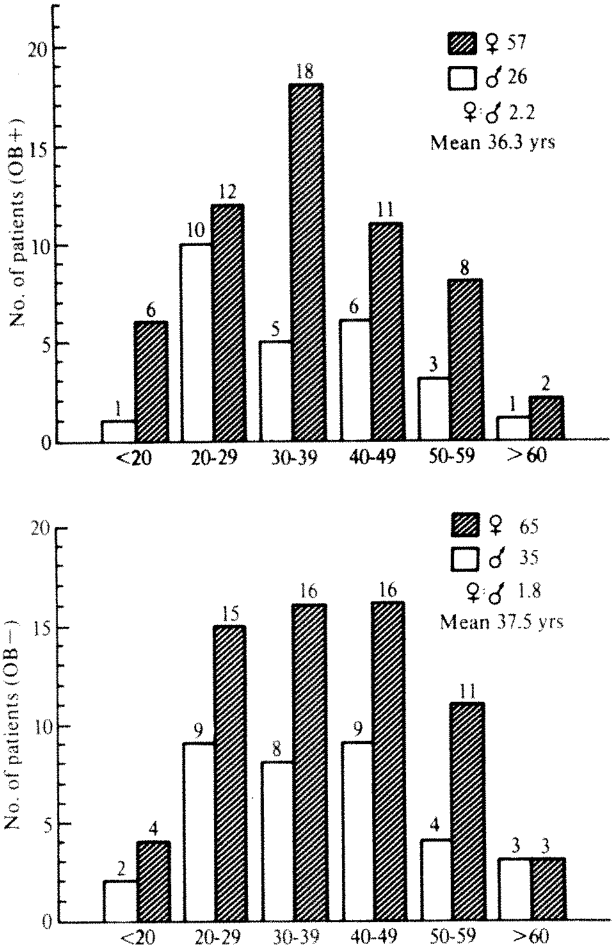

FIG. 2A. Age at onset of disease and sex distribution in patients with 'possible' multiple sclerosis and oligoclonal banding in CSF (OB+). B, age at onset of disease and sex distribution in patients with 'possible' multiple sclerosis without oligoclonal banding in CSF (OB−).

sclerosis. Of 100 patients without OB (mean follow-up of 33.9 months), 9 patients or 9 per cent converted. This difference was significant ($P < 0.01$, $\chi^2 = 7.75$). The initial sites of involvement in those patients who developed CDMS in the OB+ and OB− groups paralleled the frequency of initial lesions seen in each group as a whole, as shown in fig. 1A, B. Table 2 also includes our results for patients who were assessed electrophysiologically. In the OB+ group, 62/83 patients had one or more of the tests indicated earlier. Of these, 39 patients or 63 per cent showed evidence of dissemination conforming to the category of 'laboratory probable multiple sclerosis' (Dales *et al.*, 1981). In the OB− group 79/100 patients had laboratory testing and of these 36, or 46 per cent had laboratory evidence of disseminated disease. These findings indicate that although patients were clinically 'possible' or had unifocal disease, substantial numbers of patients in both groups showed evidence of dissemination using electrophysiological methods. Furthermore, patients who were OB+ had significantly more electrophysiological abnormalities

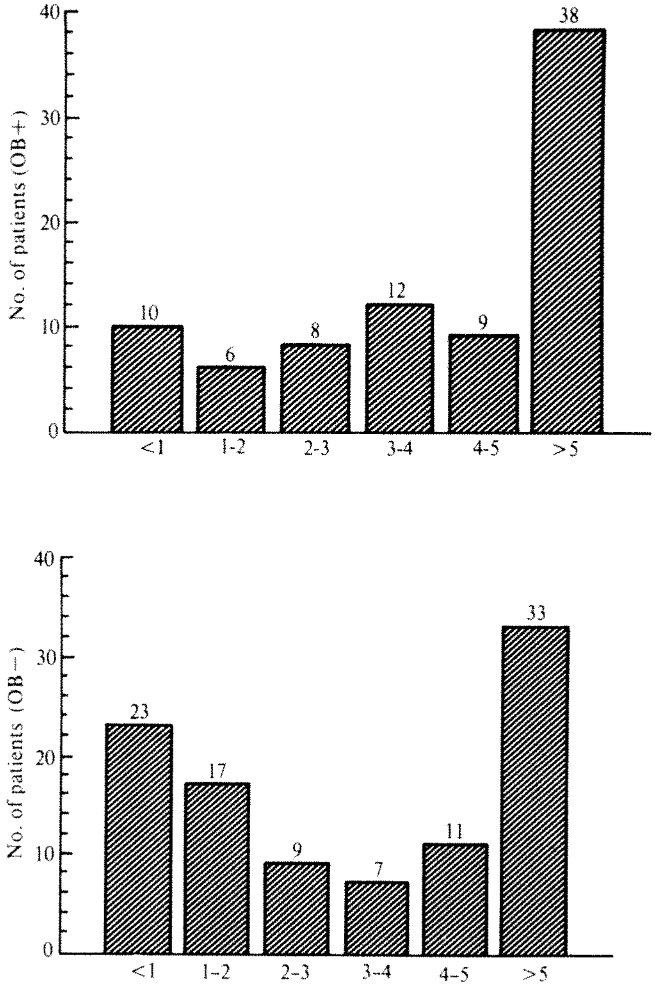

FIG. 3A. Duration of disease (yrs) in patients with 'possible' multiple sclerosis and oligoclonal banding in CSF (OB+). Mean 7 yrs 8 m. B, duration of disease (yrs) in patients with 'possible' multiple sclerosis without oligoclonal banding in CSF (OB−). Mean 5 yrs 6 m.

TABLE 2. COMPARISON BETWEEN OB* POSITIVE AND OB* NEGATIVE PATIENTS IN THE DEVELOPMENT OF DISSEMINATED DISEASE (CLINICAL AND LABORATORY)

	Percentage developing clinically definite MS	*Percentage developing laboratory probable MS*
OB+	20/83 (24 %)	39/62 (63 %)
OB−	9/100 (9 %)	36/79 (46 %)
	$P < 0.01$	$P < 0.05$

* Oligoclonal banding.

($P < 0.05$, $\chi^2 = 4.19$). There were similarly more total abnormalities in the OB+ compared to the OB− group.

DISCUSSION

A common clinical question concerns the prognosis in patients with monosymptomatic demyelination. This study suggests that the presence of OB is of predictive value in determining the likelihood of clinical dissemination. A number of immunological abnormalities, including CSF OB, have been described in patients with monosymptomatic demyelination similar to those found in patients with disseminated disease (Link *et al.*, 1973, 1976; Vandvik *et al.*, 1979). A study of 48 patients with optic neuritis showed that 95 per cent of those with OB, but only 59 per cent of those without, went on to develop probable or possible multiple sclerosis (Nikoskelainen *et al.*, 1981). Bøttcher and Trojaborg (1982) found that of 16 patients in whom both evoked potentials and IgG index were abnormal initially, 13 (81 per cent) had entered into a higher diagnostic class of multiple sclerosis over a follow-up of two to four years. For these reasons, and particularly in view of the well-documented association between OB and CDMS, it might have been expected that a significantly higher conversion rate to disseminated disease would be found in our OB+ group and this was indeed found. Comparison of clinical features in OB+ and OB− patients does not support the view that the two groups represent different entities. Rather marked similarities in clinical features between the OB+ and the OB− patients (age at onset, sex ratio, distribution of lesions) were found (*see* fig. 1, 2). These observations are similar to those comparing OB+ and OB− patients with chronic myelopathy (Paty *et al.*, 1979).

There was, however, an excess of evoked potential abnormalities in the OB+ group. This finding suggests some correlation between OB and the number of lesions or degree of dissemination. There are a number of facts which support this interpretation. First, our own evidence (although the information is difficult to obtain) indicates that OB not infrequently develops during the course of the disease. Our material includes 7 patients in whom conversion from OB− to OB+ has been documented (G. C. Ebers, unpublished). In 2 of these, simultaneous electrophoresis of fresh and stored CSF by the same technique demonstrated the conversion from OB− to OB+. Sandberg-Wollheim (1975) followed the subsequent clinical course of 61 patients with optic neuritis in whom CSF electrophoresis had been performed at the outset. Over a mean observation time of 2.6 years, 11 patients developed CDMS and 5 of these were found to have developed banding during the follow-up period. The only clinically significant difference that we found between the OB+ and OB− groups was a longer duration of illness in the former. These data show that the frequency of banding is higher in patients with longer duration of disease. This observation extends to 'possible' cases in a population with multiple sclerosis of late onset (Noseworthy *et al.*, 1981). Finally, it has also been claimed that the degree of CSF abnormality is correlated with the clinical course of the disease (Olsson *et al.*, 1976; Stendahl-Brodin and Link, 1980), although this is not universally found (Schmidt *et al.*, 1977). Our own autopsy experience in multiple sclerosis includes 3 cases of multiple sclerosis without oligoclonal banding on CSF electrophoresis (agarose and isoelectric focusing, Ebers *et al.*, 1983).

It is possible that the high frequency of banding early in the course of the disease reflects the fact that most lesions are clinically silent and at the time of clinical onset many lesions may already be present. A practical corollary of these observations is that repeat CSF electrophoresis during the course of the disease may be useful in obtaining laboratory confirmation of diagnosis. In practical terms, patients with monosymptomatic demyelination who have oligoclonal banding appear to have a higher risk for the subsequent development of clinically disseminated disease than those who are OB−. Further studies of this group of patients over the long term should determine more definitively the magnitude of this risk. However, the data only allow us to say that OB+ patients are more likely to develop clinical multiple sclerosis within the period of follow-up in this study. Whether all OB+ patients will ultimately develop clinical multiple sclerosis remains to be seen. It seems to us that it is still premature to tell patients with monosymptomatic demyelination and positive OB that they have multiple sclerosis, although the risk appears substantially higher than in OB− patients.

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NEUROPATHOLOGICAL STUDIES ON THE TOXIC SYNDROME RELATED TO ADULTERATED RAPESEED OIL IN SPAIN

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SUMMARY

Biopsies of muscle and sural nerves, and autopsies of patients affected by the toxic and neuromuscular syndrome produced by ingestion of adulterated rapeseed oil were studied using morphological, histochemical and ultrastructural methods. In muscle, two pathological pictures were distinguished according to their temporal sequence. In the early phase, the neuromuscular syndrome was characterized by myalgia and an inflammatory infiltration of the perimysium, the capsules of muscle spindles and intramuscular nerves. The muscle fibres exhibited small subsarcolemmal zones of fibril disintegration and accumulation of electron-dense material similar to Z bands. Areas of peroxidase activity were found in relation to the surface of many muscle fibres. In late stages there was severe neurogenic atrophy of muscle with intense endomysial fibrosis. Minimal perivascular inflammation by round cells, with no interstitial infiltrates, was finally present. The inflammatory myopathy that initially affected these patients differs from other forms of polymyositis and seems to be related to the inflammation present in other systems. The onset of denervation atrophy is secondary to the involvement of peripheral nerves which is the most salient and distinctive pathological feature of the syndrome.

The involvement of peripheral nerves was the most severe pathological feature. Perineuritis and, later, fibrosis of the perineurium were conspicuous and peculiar to this toxic syndrome. Degeneration of myelinated axons was constant in late stages. Distal nerves were more affected than proximal nerves.

In the CNS, chromatolysis of anterior horn cells and occasionally of cranial nerve nuclei, pontine nuclei and reticular neurons was found. In the brainstem, astrocytes were hypertrophic with abnormal nuclei and there was microglial proliferation in zones where chromatolysis was found.

The possibility that free radicals derived from the adulterated oil and cytotoxic complexes formed by mast-cell granules and eosinophil peroxidases might have been involved in the pathogenesis is discussed. The toxic oil was rich in linoleic acid which, by forming an excess of arachidonic acid, might have played an additional role in the pathogenesis of the lesions.

INTRODUCTION

A new toxic syndrome related to the ingestion of denatured rapeseed oil has caused more than 330 deaths and affected about 20 000 people in Spain. The clinical profile

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of this disease has varied since the first cases appeared in May 1981. Two clinical phases were noted, the first dating from May to June/July 1981 and being characterized by general symptoms including fever, headaches, skin rash, pruritus, cough and dyspnoea. The most frequent abnormalities found in laboratory investigations were eosinophilia, altered liver enzymes, high triglyceride levels and occasional thrombocytopenia.

The beginning of the second clinical phase, after June/July 1981, was heralded by early manifestations of neuromuscular involvement such as myalgia and numbness in the limbs. There was also oedema of the face and limbs. At this stage general and respiratory symptoms usually subsided, thrombocytopenia became more frequent and there were a few instances of thromboembolism. Pulmonary hypertension was detected in a number of cases. In the following months of 1981 and subsequently, up to the present time, the patients have presented scleroderma-like lesions, sicca syndrome, dysphagia, Raynaud's syndrome, loss of weight, pulmonary hypertension and progression of the neuromuscular syndrome to muscular atrophy and weakness. Ventilatory insufficiency due to muscle atrophy was a common event in severely affected patients. Serum IgE has been elevated in approximately 30 per cent of the cases throughout the illness. There has been higher incidence in females than in males. A few patients first exhibited neuromuscular symptoms without known respiratory or general symptoms characteristic of the first phase. The clinical features of the syndrome have been reported previously (Toxic Epidemic Syndrome Study Group, 1982).

This report describes the morphological features of the peripheral and central nervous system involvement in the syndrome based on muscle and sural nerve biopsy studies and on 20 autopsied cases with complete neuropathological examination.

MATERIAL AND METHODS

Muscle biopsies were obtained from 31 patients (8 males and 23 females) aged between 15 and 51 years. The samples were taken from the biceps (7), deltoid (2), quadriceps (3) and gastrocnemius (19) muscles 2 to 21 weeks after the beginning of overt clinical symptoms. Only 3 patients had received corticosteroid treatment (1 mg/kg/day) prior to biopsy.

Sural nerve biopsies were taken from the retromalleolar region in 73 patients (10 male, 63 female) between 3 and 71 years of age. The biopsies were taken 12 to 35 weeks after onset of the clinical illness. Twenty-seven patients had received prior treatment with steroids. In 16 patients a second sural nerve biopsy (from the contralateral side) was taken 54 to 91 days after the first. During this interval, 6 patients were given an anti-free radical treatment with superoxide-dismutase (8 mg i.m. twice daily for three weeks, followed by 8 mg i.v. per day for up to two months). Seven patients received only corticosteroids.

Autopsies from 20 cases were studied, 6 males and 14 females, aged between 10 and 68 years, and after 2 to 31 weeks of evolution. The brain, spinal cord, sciatic, tibial, common peroneal and sural nerves were studied. Samples from the sural nerve were taken at the retromalleolar level, 7 cm above this point and from the contralateral nerve. Radial and intercostal nerves, dorsal root ganglia, the cervical sympathetic chain, and stellate and mesenteric ganglia were also included in the study. The following muscles were sampled for histological study: biceps, quadriceps, gastrocnemius, intercostal and diaphragm.

Samples of muscle from autopsy and biopsy were prepared for histochemistry by freezing in isopentane cooled in liquid nitrogen and then sectioned in a cryostat. The following histochemical procedures were performed: PAS, oil red O, ATPase at pH 9.4 and after preincubation at pH 4.6 and 4.3, phosphorylase, DPNH-tetrazolium reductase and succinate dehydrogenase. Sections from the muscle biopsies were incubated in DAB (diaminobenzidine) to study the activity of peroxidases. This reaction was also studied after incubation at 37° C for ½, 1, 2 and 6 h in different solutions prepared in deionized distilled water containing 1% and 5% tocopherol acetate, 20% ascorbic acid, 1% methionine, 1% methionine with 1% ascorbic acid, 1% methionine with 1% tocopherol acetate, 1% methionine with 1% ascorbic acid and 1% tocopheral acetate, 10% PVP, EDTA in saturated solution, saturated KCN solution, sodium azide in saturated solution, 1 M glucose, 20% albumin, gelatine, and graded solutions of NaCl at concentrations ranging from 0.1 to 1 M. The incubation tests were done to check the blocking capacity of the different solutions on the activity of peroxidases. Forty-four other muscle biopsies were used as controls for the peroxidase study (cases of X-linked muscular dystrophy, polymyositis, progressive systemic sclerosis, polyarteritis nodosa, glycogenosis, mitochondrial myopathies, neurogenic atrophies of varying origin, congenital myopathy and normal adult and fetal muscle). IgA, IgG, IgE, IgM, and C3, C4 and C1q components of complement were studied by immunofluorescence on cryostat sections of 10 muscle biopsies. Parts of the tissue were fixed in 10% formalin and Karnovsky's fixative for histological and electron microscopic studies, respectively, according to conventional methods.

Fifty-four sural nerve biopsies were frozen in part for immunofluorescence studies. Both biopsies and peripheral nerves from autopsy were fixed in Karnovsky for histological, electron microscopic and teased fibre studies.

Samples from different levels of the CNS, dorsal root ganglia and autonomic ganglia were embedded in paraffin and stained with haematoxylin and eosin (HE), Nissl and Spielmeyer. Frozen sections were stained by Bielschowsky's ammoniacal-silver nitrate method for neurofibrils, Cajal's gold-sublimate for astroglia, and Del Río Hortega's silver carbonate impregnations for neurofibrils, gliofibrils and for microglia.

Biopsies from lungs, skin, liver, kidneys and placenta, as well as complete autopsies of 20 cases were studied and reported by Martínez-Tello *et al.* (1982).

PATHOLOGICAL OBSERVATIONS

Muscle Biopsies

The main pathological findings were inflammatory cell infiltration, muscle fibre atrophy and endomysial fibrosis. Inflammatory changes were evident in the first group of biopsies obtained and reached a peak of intensity between the third and fourteenth weeks of evolution of the toxic syndrome. The inflammation consisted of diffuse interstitial infiltration, predominantly of the epi- and perimysium and only occasionally in the endomysium. The infiltrates were composed mainly of mononuclear cells with occasional polymorphonuclears (fig. 1A). Eosinophils were seen in the vicinity of blood vessels. Muscle spindle capsules and the sheaths of intramuscular nerves were frequently involved as shown in fig. 1A. Vasculitis with inflammatory cell infiltration of the vessel wall was observed in veins and capillaries in 35.5 per cent of the cases after seven weeks and it became prominent in the more chronic cases (after twelve weeks). At this same time, the interstitial inflammation had decreased to a minimum.

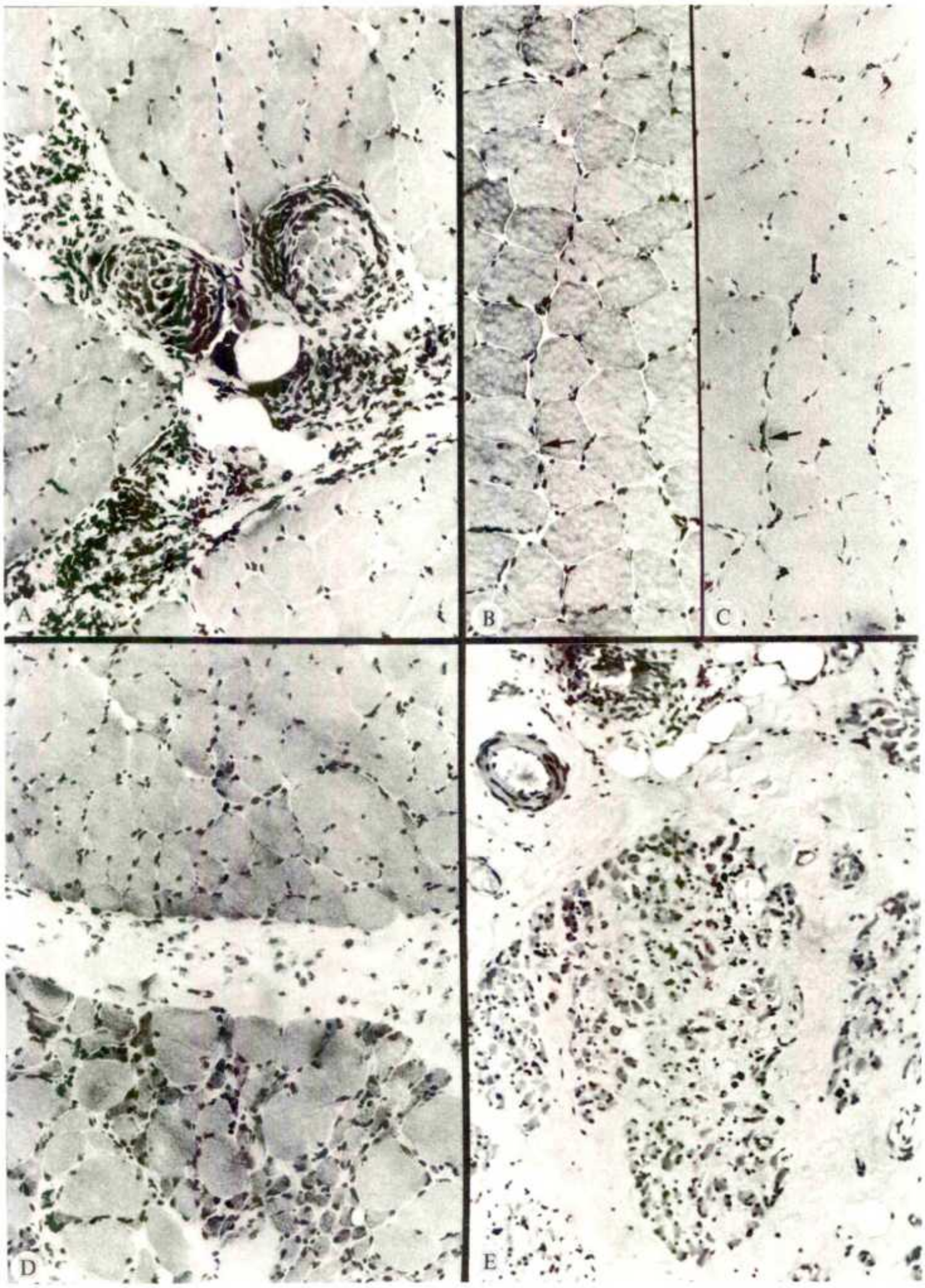

FIG. 1. *Muscle pathology*. A, muscle biopsy from the myalgic phase. There is mixed cell infiltration, predominantly mononuclear, in the perimysium. The capsule of muscle spindles and the intramuscular nerve twigs are infiltrated. Note the absence of endomysial inflammation. (HE, cryostat section, × 125). B, same phase. Small basophilic areas are present at the periphery of some muscle fibres (arrows) (HE, cryostat section, × 125). C, serial section including the same field as in B. The section was incubated in diaminobenzinde (DAB) and demonstrates black precipitate indicating peroxidase activity at the surface of several muscle fibres (arrows) (DAB, cryostat section, × 125). D, muscle biopsy from the early phase of neurogenic atrophy. Small groups of atrophic fibres are scattered within both fascicles. Atrophy is more prominent in the lower fascicle (HE, cryostat section, × 125). E, paraffin section of muscle at autopsy showing an advanced stage of atrophy involving several fascicles and with marked endomysial fibrosis (HE, paraffin section, × 125).

High endogenous peroxidase activity was present in neutrophils and in free deposits at the surface of muscle fibres (fig. 1C) in the first 13 cases which came to biopsy up to the ninth week of evolution. Inhibition tests to peroxidases were carried out as described previously. The enzyme activity was inhibited only by preincubation in 1 M NaCl (fig. 2A, B). None of the 44 control cases had peroxidase activity in relation to muscle fibres. Only those cases that had inflammatory cell infiltrates showed a positive reaction, restricted to inflammatory cells. In HE preparations, irregular superficial basophilic zones in the muscle fibres corresponded with the surface areas exhibiting peroxidase activity (fig. 1B).

In addition to the changes described above, almost all the cases initially had atrophy of isolated fibres. The affected fibres were histochemically type II and presented inversion of the oxidative enzyme reaction. Denervation atrophy became clear and prominent after eighteen weeks of illness (fig. 1D). The severity of the atrophy varied somewhat from one fascicle to another. At late stages, endomysial fibrosis, separating the atrophic fibres, became prominent (fig. 1E).

Electron microscopic examination of muscle biopsies taken during the earlier phases revealed multiple focal changes in muscle fibrils (fig. 2C). These changes consisted of disorganization and streaming of the Z band and the appearance of electron-dense material similar to the Z band mixed with myofibrils, especially at the periphery of muscle fibres. Here they formed dense irregular aggregates underneath the sarcolemma. Two or more sarcomeres of adjacent myofibrils could be affected. Another abnormality found in the same or different fibres was the presence of collections of lysosomes, vesicles and lamellar bodies forming myelin-like figures in intermyofibrillar spaces. The inflammatory infiltrates were formed mostly by lymphocytes and macrophages with occasional neutrophils. Although intact eosinophils were not found with the electron microscope, dense granules with the characteristic crystalline core were occasionally seen in the extracellular space adjacent to muscle fibres. (fig. 2D).

The atrophic fibres, isolated or in groups, had similar ultrastructural features: folds of redundant basal lamina, loss of myofilaments, and frequent membrane-bound vesicles and dense bodies between the fibrils.

Nerve Biopsies

The earliest and most common abnormality was the presence of inflammatory infiltrates around veins and capillaries in the epineurium and was seen in 68 cases (93.1%). These infiltrates were also seen diffusely in the endoneurial interstice (50% of cases) and occasionally also around endoneurial capillaries (33%) (fig. 3A).

Frequently there was round cell infiltration of the perineurium (46 cases, 63%). It began focally and later extended to the whole circumference of the perineurium, resulting in thickening and loosening of the perineurial cell layers. Each fascicle was involved to a different degree and sometimes intact perineurium was found adjacent to other fascicles with marked perineuritis.

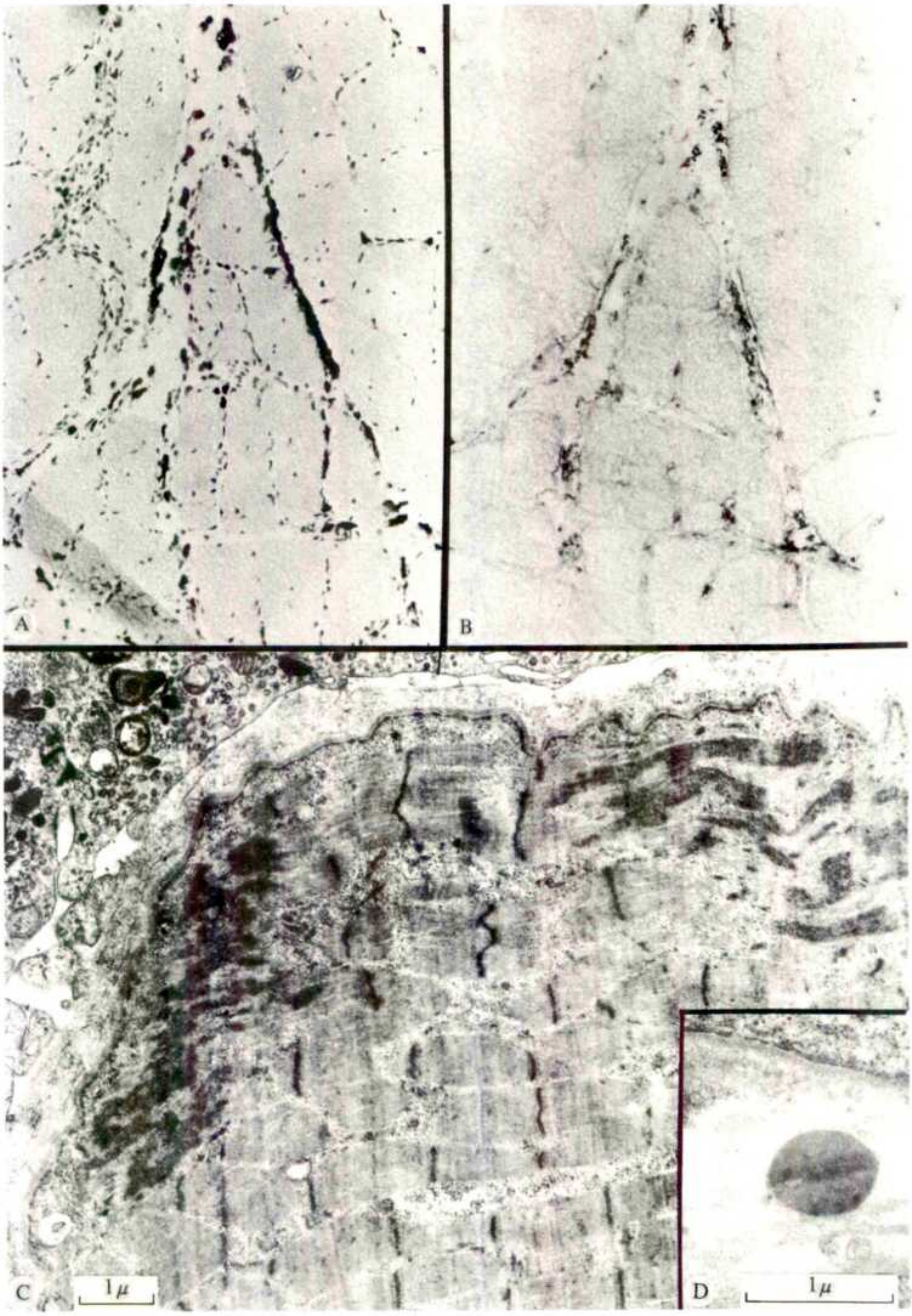

FIG. 2. *Muscle pathology: histochemistry and ultrastructure.* A, muscle biopsy from the myalgic phase. A cryostat section, unfixed and incubated in DAB, demonstrates peroxidase activity (black precipitate) at the surface of muscle fibres (DAB, × 125). B, serial section of the same biopsy preincubated in 1 M NaCl prior to DAB test. The blocking effect of 1 M NaCl on the activity of peroxidase is shown (same field as in A) (DAB after preincubation with 1 M NaCl, × 125). C, electron micrograph of muscle fibre showing irregular subsarcolemmal aggregates of electron-dense material similar to Z bands, and focal disorganization of myofibrils. These changes were present at the stage of inflammatory myopathy (× 11 300). D, small bodies with the ultrastructural features of eosinophilic granules (well circumscribed ovoid granules with a granular matrix and a central band constituting a crystalline core) were occasionally found lying free in the extracellular space alongside muscle fibres (× 26,880).

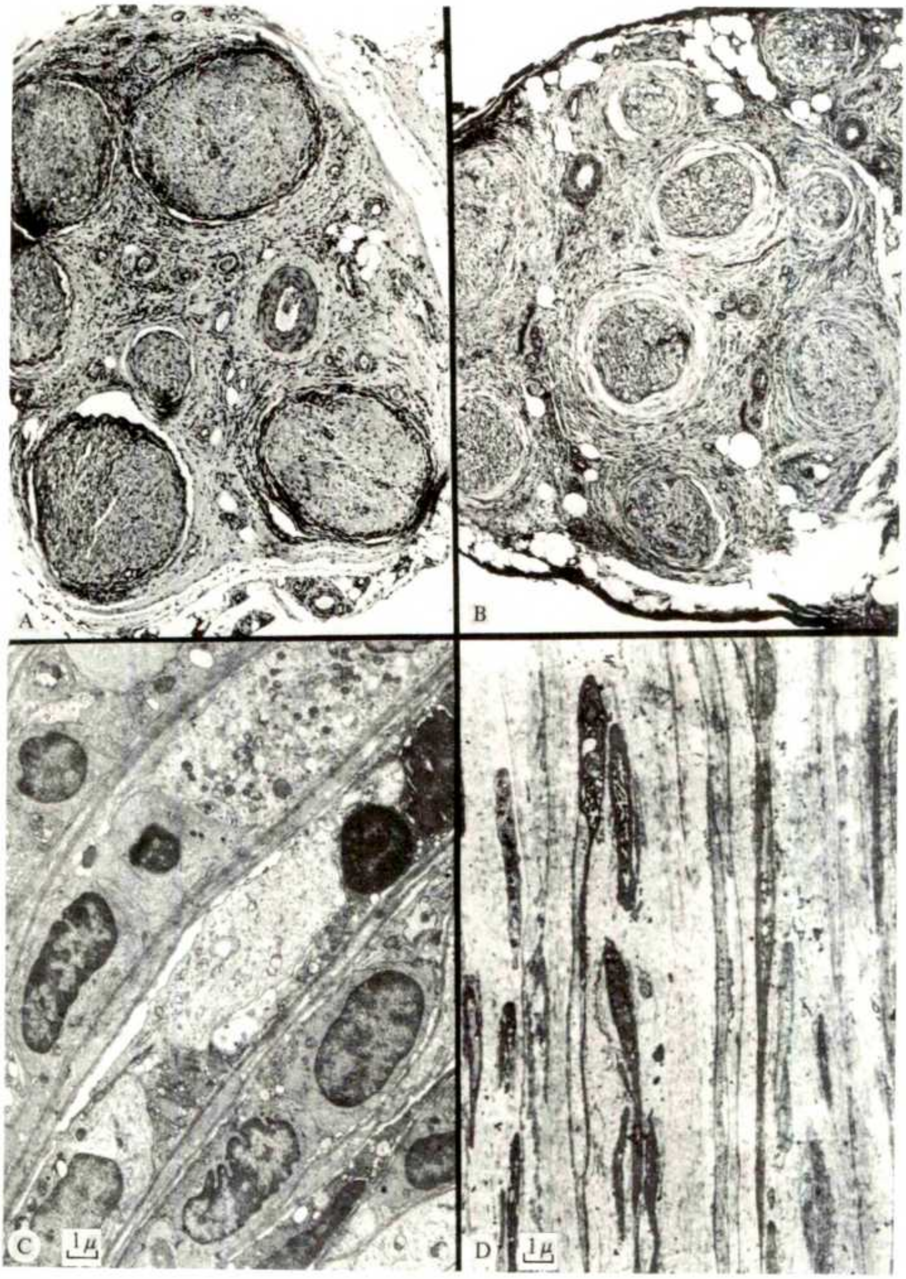

FIG. 3. *Sural nerve: histology and ultrastructure.* A, transverse section of sural nerve illustrating typical histological findings, with mononuclear inflammatory cells infiltrating epineurium and epineurial veins and capillaries. A pronounced perineuritis is present around most fascicles. Minimal endoneurial inflammation (HE, × 25). B, later stage showing perineurial fibrosis of variable intensity around each fascicle (HE, × 25). C, electron micrograph of perineurium at the stage of perineuritis. Inflammatory cells are present between perineurial layers. Fibroblasts are seen amongst them (× 4800). D, electron micrograph of thickened fibrosed perineurium. There is loss of perineurial cells, with fibroblastic infiltration and marked deposition of collagen (× 4800).

In addition to perineuritis in 29 cases (39.7%) there was fibroblastic proliferation in the perineurium. This was more evident in cases with less cell infiltration. The fibrosis varied from focal to generalized involvement of the whole perineurium, and from one fascicle to another, as did the inflammatory process (fig. 3B).

The epineurial arteries were narrowed by subendothelial fibrosis in 15 per cent of the cases. In no instance did inflammatory cells invade the arterial wall. The arteries were examined for 0.5 to 1 cm of their length in step sections. It could be seen that subendothelial fibrotic plaques were focal. This finding bore no relation to age.

The immunofluorescence studies carried out on frozen nerve sections gave no consistent results with regard to deposition of immunoglobulins (IgA, IgG, IgM, IgE), fibrinogen or complement components (C1q, C3 and C4) in epineurial vessel walls or other nerve structures.

Abnormalities of nerve fibres were found in all cases by the examination of thin sections and/or teased fibre preparations. In the latter, the most common finding was the presence of linear ovoid segmentation of the thick myelinated fibres (i.e. degeneration of wallerian type). Occasionally there was widening of the nodes with retraction of paranodal myelin, and segments devoid of myelin. Demyelinated segments were usually consecutive and not intercalated. Degenerated fibres with myelin and axonal homogenization were confirmed in 1 μm thick sections. Abnormal fibres were distributed focally in the fascicle, usually showing a topographical relationship with affected areas of the perineurium (fig. 4A). In advanced cases in which there was fibrosis of the entire perineurium, fibre degeneration was generalized and macrophages were present. A few groups of thin myelinated fibres seemed preserved (fig. 4B).

The ultrastructural study of the perineurium showed proliferated fibroblasts even in the early stages of perineuritis. At the light microscope level this change was masked by the inflammatory cell infiltration. The inflammatory cells had ultrastructural features similar to those of T lymphocytes regarding nuclear morphology and concentration of organelles. Fibroblasts contained abundant and dilated rough endoplasmic reticulum. Between these cells there were macrophages sometimes lying next to cells with basal laminae (perineurial cells). Frequently, thick loose basement membranes were seen in the perineurium. There was loss of perineurial cells (fig. 3C, D). In the nerve fascicles there was constant acute degeneration of axons and some fibres with an increase of intra-axonal filaments. Thick myelinated fibres were usually affected, while thin myelinated and unmyelinated fibres were relatively preserved (fig. 4C). In advanced cases, besides perineurial fibrosis, there was also marked endoneurial fibrosis and redundant basement membranes.

The pathological changes described above are in keeping with the severity of the clinical syndrome (Table 1) while the incidence and degree of histological changes are greater in untreated cases than in those treated with corticoids.

Sural nerve biopsies were repeated on the contralateral side in 16 patients 54 to 91 days after the first biopsy. Three of these patients were untreated during this time interval. Six of them were treated with superoxide-dismutase and 7 with

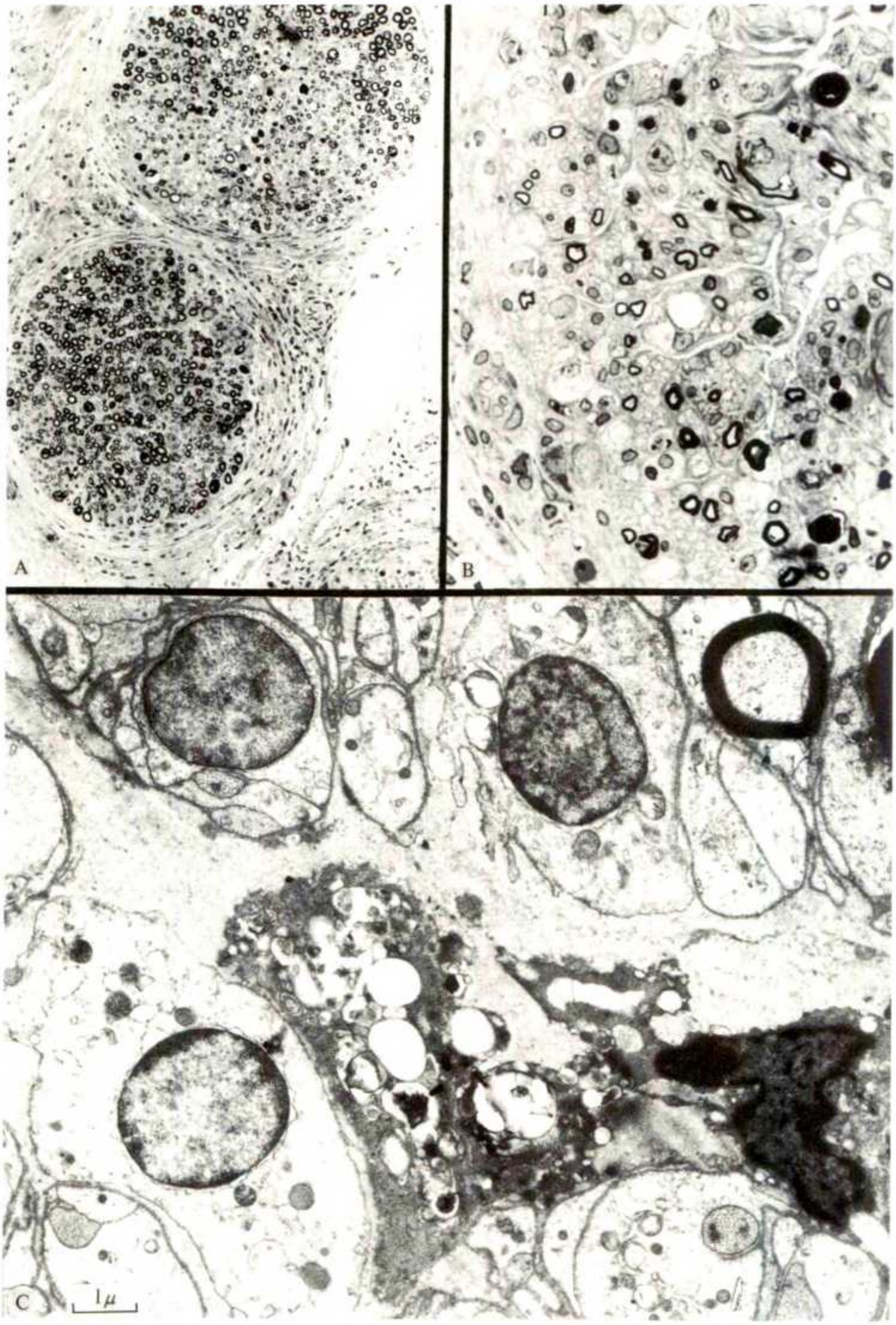

FIG. 4. *Sural nerve pathology*. A, epon section demonstrating uneven involvement of two adjacent nerve fascicles. There is pronounced patchy fibre loss in the upper fascicle and moderate scattered fibre loss in the lower fascicle. (Toluidine blue, × 125). B, area of fibre loss mostly involving thick myelinated fibres; a few small myelinated fibres remain. (Toluidine blue, × 1250). C, electron micrograph of sural nerve illustrating loss of fibres; a single myelinated fibre and several unmyelinated fibres are present. Part of a macrophage containing vacuoles and myelin debris is seen. There is increase of endoneurial collagen (× 11,200).

corticosteroids prior to the second biopsy. The comparative results are given in Table 2. Both untreated and treated cases showed a tendency to diminished inflammation and increased fibrosis with time.

TABLE 1. SURAL NERVE: PATHOLOGICAL FINDINGS IN RELATION TO THE CLINICAL SYNDROME

Clinical syndrome	*Slight*		*Severe*	
Corticosteroid treatment	No	Yes	No	Yes
Evolution (weeks)	15–31	12–35	18–31	16–35
No. of cases	25	9	21	18
Inflammatory infiltration	21(84%)	8(88.8%)	21(100%)	18(100%)
Perineuritis	15(60%)	3(33.3%)	20(95.2%)	8(44%)
Perineural fibrosis	4(16%)	1(11.1%)	15(71.4%)	9(50%)

TABLE 2. SEQUENTIAL STUDY OF HISTOPATHOLOGICAL CHANGES IN SURAL NERVES

Treatment	*None*		*SoD**		*Corticosteroids*	
No. of cases	*3*		*6*		*7*	
Biopsy	*1st*	*2nd*	*1st*	*2nd*	*1st*	*2nd*
Inflammatory infiltration	3	2	5	6	7	6
Perineuritis	2	0	3	2	5	2
Perineural fibrosis	1	2	1	3	3	5

* Superoxide dismutase.

Autopsy Studies

The first cases that came to be studied post-mortem were 11 which clinically had a shorter course (two to ten weeks' duration) and which did not manifest neuromuscular signs or symptoms. Death was caused by respiratory failure in 4 patients and by thromboembolism in 7. Neuropathological examination showed an acute anoxic encephalopathy in 2 cases. None of them had chromatolysis of CNS neurons which was later found in the second group of patients. Occasional unrelated findings in this group were partial aqueduct stenosis in one case, cribriform change in the basal ganglia in 2 cases aged 48 and 52 years, a microscopic cortical infarct probably of embolic origin in one case aged 31 years, arteriosclerotic changes in cerebral vessels in one case aged 68 years and a single case with a microadenoma of the pituitary. No lesions were found in peripheral nerves or skeletal muscle.

The following 9 autopsy cases were from patients who had had a protracted illness and had developed a severe neuromuscular syndrome (second clinical phase). Death in all cases was due to respiratory failure and/or sepsis. Neuropathologically, 4 cases had cerebral lesions related to anoxic encephalopathy. Microscopic changes consisted of diffuse cortical neuronal changes such as ischaemic cell change, neuronal shrinkage and pyknosis with some areas of intracortical laminar sponginess. In 2 cases there was also severe involvement of neurons of thalamus, putamen, pallidum and Ammon's horn and Purkinje cells of the cerebellum. One of the cases, aged 10 years, had areas of laminar neuronal loss suggesting that the anoxic encephalopathy had had a more chronic course. This child also had a cortical infarct involving two convolutions of the occipital convexity that could be related to local vascular pathology: three small to medium-sized meningeal arteries overlying the infarcted area had abnormal vessel walls due to subendothelial thickening and disorganization with replication of the elastica. Two of these arteries were patent, but the smallest one was occluded. There were no arteriosclerotic changes in other cerebral vessels. Focal vascular changes, unrelated to age, such as those seen here, were described by Martínez-Tello *et al.* (1982) in general autopsies of toxic syndrome patients. One of the 4 cases in this group had associated acute disseminated septic microinfarcts in brain and brainstem. The general autopsy confirmed an acute bacterial endocarditis.

The most consistent neuropathological finding in all 9 cases of this second group was central chromatolysis of anterior horn cells. This change was most conspicuous in the lateral neuronal groups of the lumbar cord. In 2 cases, chromatolysis was very severe and associated with cytoplasmic vacuolation (fig. 5A). Five cases had in addition chromatolytic changes in brainstem neurons (fig. 5B). In 2 the brainstem changes were widespread and severe, including several tegmental nuclei (central and lateral nuclei of the medullary reticular substance, cranial nerve nuclei of the sixth, seventh and eighth nerves and the locus coeruleus) and the grey nuclei of the basis pontis. Chromatolytic changes were associated with focal microglial nodules surrounding occasional necrotic neurons (fig. 5B, C) and with local astrocytic proliferation at the level of the reticular substance of the medulla and in the basis pontis. Some astrocytes had large bizarre irregular nuclei and plump chromatin granules (fig. 5D). In 3 of the cases the brainstem changes were scattered and confined to chromatolysis of one or two of the above mentioned tegmental nuclei, sparing the pontine nuclei and without microglial or astrocytic reaction. The middle cerebellar peduncles, cerebellar cortex and corticospinal pathway were unaffected.

The dorsal root ganglia and motor and sensory spinal roots were not abnormal by conventional histological techniques.

Pathological findings in skeletal muscle were similar to those encountered in the biopsies. Inflammatory infiltration was slight in muscle and absent in some cases. Infiltration of veins and capillaries was present. These two changes were much less apparent than in the biopsies. There was severe denervation atrophy involving whole fascicles in every case. It was always accompanied by endomysial fibrosis. Distal muscles were more involved than proximal ones, and lower limb muscles were more severely damaged than those of the upper limb. Gastrocnemius was usually the most affected. Intercostal muscles examined in 2 cases were affected to the same extent as the proximal muscles of the upper limbs (biceps). The diaphragm examined in one case was affected to the same extent as other muscles but not as severely as the gastrocnemius.

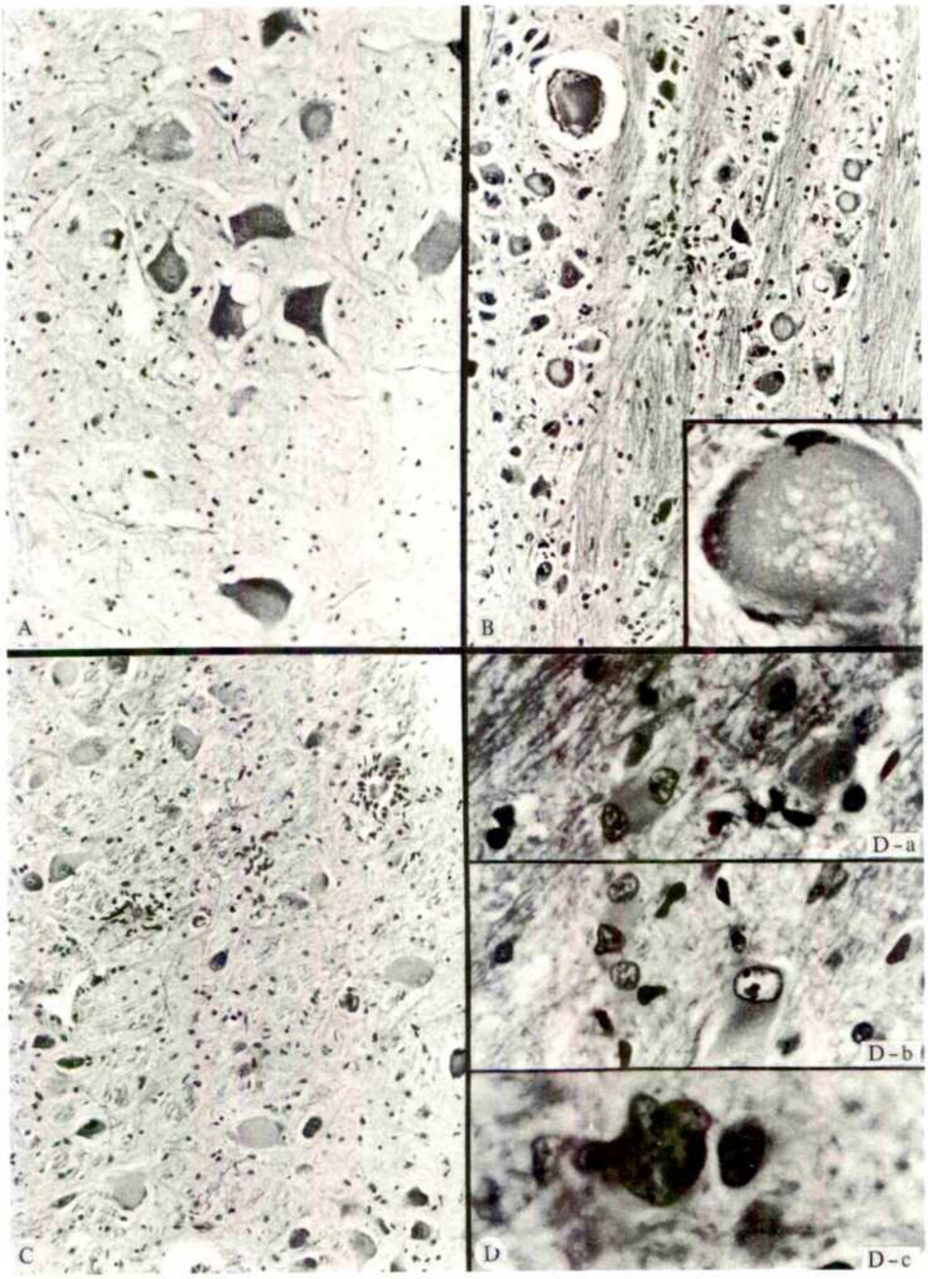

FIG. 5. *Central nervous system pathology.* A, section showing lumbar anterior horn neurons. There is central chromatolysis together with fine and gross vacuolar changes. (HE, × 125). B, chromatolytic changes in neurons of the basis pontis. An enlarged chromatolytic neuron with fine cytoplasmic vacuolization is shown in inset (HE, × 125; *inset* × 1250). C, medullary reticular substance nucleus with widespread chromatolysis. Three small microglial nodules centred around necrotic neurons are shown (HE, × 125). D, astroglial proliferation with binucleate forms (a) and irregular and bizarre nuclei (b, c) in the brainstem (HE: (a) × 500; (b) × 500; (c) × 1250).

The lesions previously described in biopsied sural nerves were also found in sensory and motor nerves of the last 9 autopsied cases. They were more intense in distal nerves of the lower limbs. The sural nerve was more affected at the retromalleolar level than 7 cm above it. The sciatic nerve was less affected at the greater sciatic foramen than the tibial nerve. There were asymmetries with regard to the severity of the pathology on the two sides of the body. Intercostal nerves were also affected.

DISCUSSION

The neurological manifestations of the toxic syndrome due to the ingestion of adulterated rapeseed oil (Tabuenca, 1981; Casado-Flores *et al.*, 1982) involve muscles, peripheral nerves and the central nervous system.

Changes in Muscle

In the muscles, histopathological changes begin to appear in the clinical phase of myalgia. These changes are characterized by an inflammatory myopathy with lymphocytic cell infiltration and occasional neutrophils with an epi- and perimysial involvement. This lesion is different from polymyositis and myositis associated with connective tissue disorders in that there is no endomysial infiltration (Vilppula, 1972) and frank necrosis or regeneration of muscle fibres is absent (Adams, 1973). The inflammatory myopathy of the toxic syndrome has a tendency to late fibrosis and in that sense it may resemble fibromyositis (Adams, 1975), although neither the clinical nor the histological picture (absence of nodules, not self-limiting) corresponds to it. The quality and the topography of the inflammation in the toxic syndrome is similar to that observed in eosinophilic fasciitis (Barnes *et al.*, 1979). The high eosinophilic counts in blood are in accordance with this picture. In spite of the high eosinophilic counts in peripheral blood, and of the presence of numerous eosinophils inside muscle vessels, they are virtually absent from the tissues themselves. This is also common in eosinophilic fasciitis (A. S. Fauci, personal communication, 1981). An observation, however, that is quite characteristic in the toxic syndrome is the inflammatory infiltration of nervous structures in muscles (nerve bundles and muscle spindles).

The electron microscopic study of muscle biopsies disclosed granules in the interstitium that have the ultrastructural features of eosinophilic granules (Zucker-Franklin, 1980). From this it could be assumed that eosinophils might have released their granules or become autolysed as is known to occur in antiparasitic reactions and in some experimental systems (Watanabe *et al.*, 1977; Klebanoff *et al.*, 1980). It is known that the major basic protein is contained in the crystalline core of the granules and that it can damage tissues in the appropriate concentrations (Gleich *et al.*, 1980).

The high extracellular activity of peroxidase could be explained by its release from neutrophils or eosinophils. Our inhibition tests, incubating muscle sections with albumin, cyanide, azide and other agents, produced no significant drop in enzyme activity. In our muscle sections peroxidase activity was significantively decreased with 0.5 M NaCl and completely inhibited with 1 M NaCl. This resembles the behaviour of the complex mast-cell granule-eosinophil peroxidase (MCG-EPO), described by Klebanoff *et al.*, (1980). We take this as evidence in favour of the eosinophilic origin of the peroxidase activity and perhaps for the presence of the MCG-EPO complex. Superficial non-necrotic lesions observed at the surface of the muscle fibres could be related to the peroxidase activity observed in the toxic syndrome. Other eosinophilic components, such as major basic protein, are cytotoxic and damage the cell membranes in asthma (Gleich *et al.*, 1980) and in tissue culture.

Later in the course of the disease, atrophy of muscle fibres supervenes. Initially it involves single fibres. The histochemical features are those of denervation atrophy (Dubowitz and Brooke, 1973). It is followed by group atrophy. This denervation process is related to early involvement of intramuscular nerves. It foreshadows the severe degree and form of involvement observed later in major peripheral nerve trunks. Intense endomysial fibrosis is established in advanced stages. It surpasses the degree and bears no topographic relation to the inflammatory process, which only rarely affects the endomysium. It is possible that the endomysial fibrosis is part of a process of general fibrosis, also observed in the perineurium and skin. Activated fibroblasts with intracytoplasmic inclusions, similar to those of infantile digital fibromas, have been seen in skin biopsies of the toxic syndrome (Conde-Zurita, 1982).

As the disease process evolved, the inflammation decreased in muscle and became restricted to the blood vessels, seen as small perivascular infiltrates or invading the vessel wall. It was present in veins and capillaries. Arteries were not involved. This capillary and venous vasculitis observed in muscle is like that observed elsewhere in the body (Martínez-Tello *et al.*, 1982). The initial cutaneous venulitis due to immune deposition is similar to the process that we describe (Soter, 1980). Immune complexes were investigated in the toxic syndrome in tissue sections and in blood with inconsistent results (Servicio de Inmunología de la Fundación Jiménez Díaz *et al.*, 1982). Fibrinoid necrosis of vessel walls, which is seen in vasculitides due to immune complexes, was not found in our cases. There are also morphological analogies between the vascular changes in the toxic syndrome and those seen in rejected organs (Porter, 1974); moreover, the kind of cells which form the inflammatory infiltrate—macrophages and lymphocytes—are similar to this situation.

Peripheral Nerve Involvement

Involvement of peripheral nerves was detected early in intramuscular nerve fascicles and verified later in major nerves at a time when there were signs of peripheral sensorimotor neuropathy. From the histopathological standpoint, the neuropathy always had an inflammatory character. Venocapillary lymphocytic infiltrates of the epi-, peri- and endoneurium without fibrinoid necrosis were commonplace. Perineuritis due to lymphocytic infiltration of the perineurium was the salient pathological feature. It is difficult to find other conditions with a histological picture similar to this neuropathy, except in a general disease such as sarcoidosis (Oh, 1980) or as reported in a single case of progressive systemic sclerosis (Richter, 1954). As far as we know, there is only one other instance which resembles this condition. Asbury *et al.* (1972) described two patients with sensory perineuritis. The inflammatory involvement with later fibrosis of certain fascicles and secondary changes in nerve fibres is similar to the picture that we have observed. In their cases, involvement was restricted clinically to sensory nerves while in our material it was always of sensorimotor distribution. These authors suggested an immunoallergic mechanism for sensory perineuritis. We have found only occasional deposits of immune complexes with no definite pattern in the nerves.

Perineurial fibrosis begins simultaneously with the inflammatory infiltration, suggesting that primary fibroblastic activation takes place early and fibrosis is not only the result of a scarring process.

With regard to nerve fibre damage, this was usually patchy within the fascicles, similar to the damage observed in an inflammatory neuropathy such as the Guillain–Barré syndrome (Arnason, 1975) and in vascular neuropathies, such as necrotizing vasculitis (Dyck *et al.*, 1972) and in diabetes (Sugimura and Dyck, 1982). Thick myelinated fibres were the most vulnerable and unmyelinated fibres more resistant. This pattern has been observed in ischaemic and compression neuropathies. Besides some instances of isolated myelin damage, the most common changes were consistent with acute axonal damage commonly observed in processes with axonal interruption.

CNS Involvement

The anoxic encephalopathy present in 6 cases that died during the first and second clinical phases of the disease correlates with the respiratory failure and shock that these patients had terminally.

Central chromatolysis was a common finding in anterior horn cells and several cranial nerve nuclei; it could usually be related to peripheral nerve damage (axonal reaction). In the last few cases there was, however, chromatolysis in other brainstem nuclei (pontine grey, medullary reticular substance), which could not be explained in terms of anterograde or retrograde degeneration. It was accompanied in 2 cases by local gliosis, astrocytes with atypical nuclei, microglial infiltration and neuronophagia. It is tempting to speculate that these isolated neuronal lesions might be primary and perhaps related to a toxic effect on nucleic acids. Chromatolytic changes have been described in pellagra (Ishii and Nishihara, 1981). These patients had no clinical evidence of pellagra or other associated vitamin deficiencies.

Pathogenetic Interpretation

The neuropathological changes have several features in common with those observed in the rest of the body (Martínez-Tello *et al.*, 1982). They can be summarized as follows: (1) endothelial lesions, early and generalized, followed by fibrosis and stenosis of arterial lumen; (2) diffuse interstitial inflammation involving mainly lung, skin and muscle, accompanied by eosinophilia and high serum levels of IgE; (3) generalized vasculitis involving veins and capillaries, with intense perineuritis; (4) fibrosis manifested particularly in skin, muscle and perineurium. These lesions need to be explained by a unifying pathogenetic hypothesis. We feel that free radicals and precursors of arachidonic acid in the toxic oil may have been major factors in the initiation of the pathological events (fig. 6). The oxidation of triglycerides present in the toxic oil would give rise to the production of various free radicals. This oil has been found to be very rich in peroxide (A. M. Michelson, personal communication, 1982). Denaturation with 2 per cent aniline, refinement, deodorization, and storage in clear and porous containers may have enhanced this

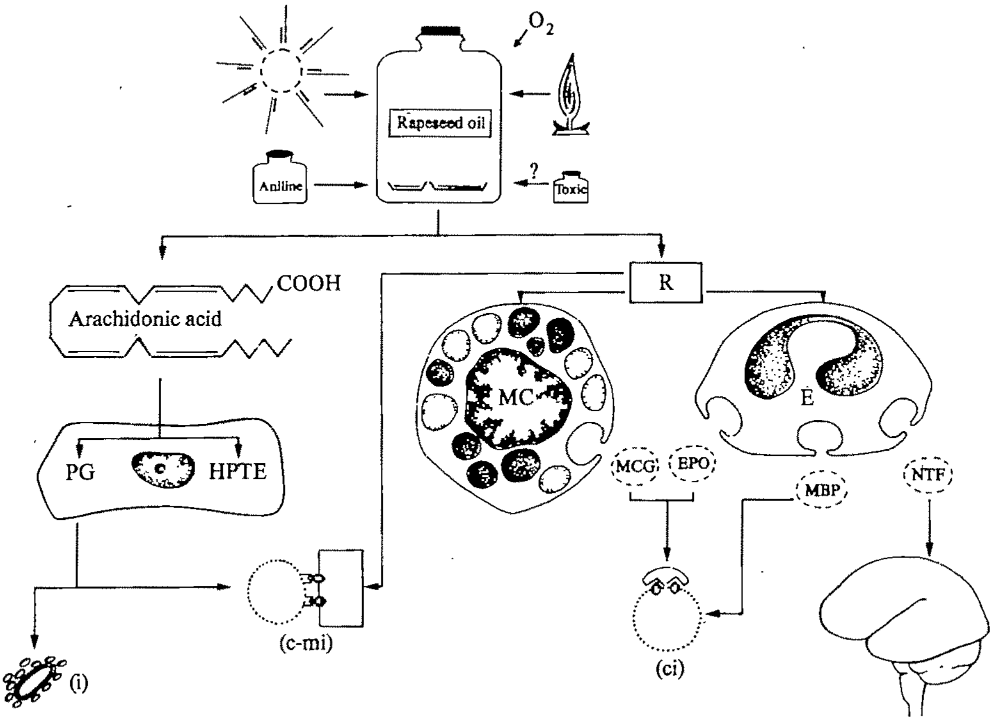

FIG. 6. Possible mechanisms that may be implicated in the pathogenesis of the toxic syndrome. Rapeseed oil is rich in polyunsaturated fatty acids which when exposed to added anilines (denaturation) or heat (refinement and deodorization), or to light and oxygen (transparent and porous containers), and when stored for prolonged periods, liberate arachidonic acid and free radicals (R). These two compounds can damage cell membranes, inducing an immune reaction. One action of free radicals is to induce degranulation of mast cells (MC) and eosinophils (E) causing liberation of mast cell granules (MCG) and eosinophilic peroxidases (EPO), major eosinophilic basic protein (MBP) and eosinophilic neurotoxic factor (NTF). HPTEs (*see* text) are intracellular metabolites of arachidonic acid and can be another factor favouring mobilization of eosinophils. Prostaglandins (PG) are formed from arachidonic acid and, in turn, may cause inflammation (i) as well as regulate immune reactions. Delayed cell-mediated immunity (c-m i) can be induced directly by free radicals and enhanced by prostaglandins. Cytotoxic type autoimmunity (ci) could be generated by R through the cytotoxic activity of MBP and MCG-EPO complexes. The eosinophil neurotoxic factor (NTF) may damage the nervous system directly.

process (Vioque, 1982). The oil is also rich in precursors of arachidonic acid. This binds to albumin in plasma and is incorporated in membrane phospholipids. Damage to cell membranes in vascular endothelium and muscle could thus be explained through the action of arachidonic acid and free radicals (Del Maestro *et al.*, 1980).

Tissues rich in mast cells such as lung, skin and peripheral nerve may have been more prone to damage if we assume a role for MCG-EPO complexes. The paucity of glutathione in muscle could explain its liability to damage; this substance exerts a protective role against the action of peroxides and free radicals. (Meister, 1981). The intracellular metabolism of arachidonic acid gives rise to hydroperoxyeicosatetraenoic acids (HPTE) and prostaglandins. Both may have had a role in thromboembolic events in the first two stages of the disease. Mono-HPTE has a chemotactic action for eosinophils (Goetzl, 1980). Prostaglandins mediate inflammation and modulate many biological process, such as cell-mediated immunity, and autoimmune reactions may have taken place, such as is described in gold salts intoxication (Sterman and Schaumburg, 1980). Lastly, the action of peroxides could also explain the generalized fibrosis, through the activation of fibroblasts and the formation of insoluble collagen (Brawn and Fridovich, 1980).

Other possible toxic factors in the oil such as anilides have been incriminated. However, the experimental neuropathological disease induced by anilides is different from the human disease (Pestaña, 1982). High levels of IgE in serum have been found, although any evidence of any specificity to antigens in rapeseed oil is lacking (Brostoff *et al.*, 1982). The clinical and pathological findings do not resemble those present in allergic diseases.

ACKNOWLEDGEMENTS

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SPEECH FLUENCY IN CROSSED APHASIA

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SUMMARY

Three strongly right-handed patients developed fluent aphasia after right hemisphere infarction documented by computerized tomography. For these patients and for other reported cases of crossed aphasia suitable for analysis, the correlation between fluency and infarct localization was similar to that of right-handed aphasics with left-sided lesions. Right hemisphere language representation in most crossed aphasics probably mirrors that normally present in the language-dominant left hemisphere.

Two of these patients showed concomitant hemispatial inattention and visuoconstructive impairment. Right hemisphere language dominance therefore does not preclude ipsilateral specialization for visuospatial functions.

INTRODUCTION

Aphasia from a right cerebral hemisphere lesion in right-handers (crossed aphasia) is rare (Roberts, 1951; Gloning *et al.*, 1969; Hécaen *et al.*, 1971). Regardless of lesion site, crossed aphasia (CA) has been characterized as nonfluent, implying that when the right hemisphere is anomalously language-dominant, language organization does not mirror that normally present in the left hemisphere (Angelergues *et al.*, 1962; Brown and Hécaen, 1976; Urbain *et al.*, 1978). This paper describes three patients in whom persistent fluent language disturbances followed right cerebral infarction confirmed by computed tomography. For these three cases and for other reported CA patients, the correlation between fluency and infarct localization was similar to that of right-handed aphasics with left hemisphere lesions. For most right-handed adults, intrahemispheric representation of language functions probably does not depend on the side of language dominance.

CASE SUMMARIES

Case 1

A 51-year-old college educated man had a sudden onset of disturbed speech and difficulty using his left hand. There was no prior history of neurological illness. He spoke only English. He was strongly right handed (laterality quotient of 100 on the Edinburgh Inventory of handedness—Oldfield, 1971), and 7 out of 8 first degree relatives were right handed. Detailed evaluation was made three weeks after onset. By the time of discharge two weeks later he had improved slightly, and similar deficits were apparent when he was later seen as an outpatient.

Visual fields, ocular movements and optokinetic nystagmus, tactile sensation, motor tone and strength, and gait were normal. There was no unilateral visual or tactile neglect. On the left, he showed clumsy fine finger movements, a pronator drift of the outstretched arm, hyperreflexia and Babinski's sign.

He was alert and orientated. Affect was normal. Immediate recall (oral repetition span) was four digits. Each of three previously rehearsed object names was recalled after a five minute delay.

Spontaneous speech was grammatical but hesitant. He showed stuttering on initial syllables, word-finding pauses and a paucity of substantive words. In describing the Boston Diagnostic Aphasia Examination (BDAE) Cookie Theft picture (Goodglass and Kaplan, 1972), he stated 'The sink is overspilling. I don't know what the little girl; she's gesturing something there'. Literal paraphasias, present during spontaneous speech, were more frequent during automatized speech, such as nursery rhyme recitation. Rate of speech, prosody, phrase length and articulation of individual phonemes were normal. Confrontation naming was mildly impaired, but mistakes were often self-corrected. Auditory comprehension was normal except when he followed commands dependent on a knowledge of syntactic relations. Repetition was impaired, particularly for syntactically complex sentences. There were literal paraphasias on phrase repetition and verbal paraphasias on number repetition. Reading aloud was similarly hesitant and paraphasic. He correctly spelled words aloud but failed to name most words spelled aloud to him. His BDAE aphasia severity rating was 4 (on a scale of 0 to 5, with 5 representing the mildest deficits), and his speech profile was that of conduction aphasia (Goodglass and Kaplan, 1972) (fig. 1).

Affective intonation during spontaneous speech and repetition, assessed by the bedside method of Ross (1981), was normal. His spontaneous facial expressions and production of requested emotional expressions on command were normal. With the examiner standing behind him, he could name the affective content of the examiner's speech (Ross, 1981). Melody while singing was good, and he recognized tunes whistled by the examiner.

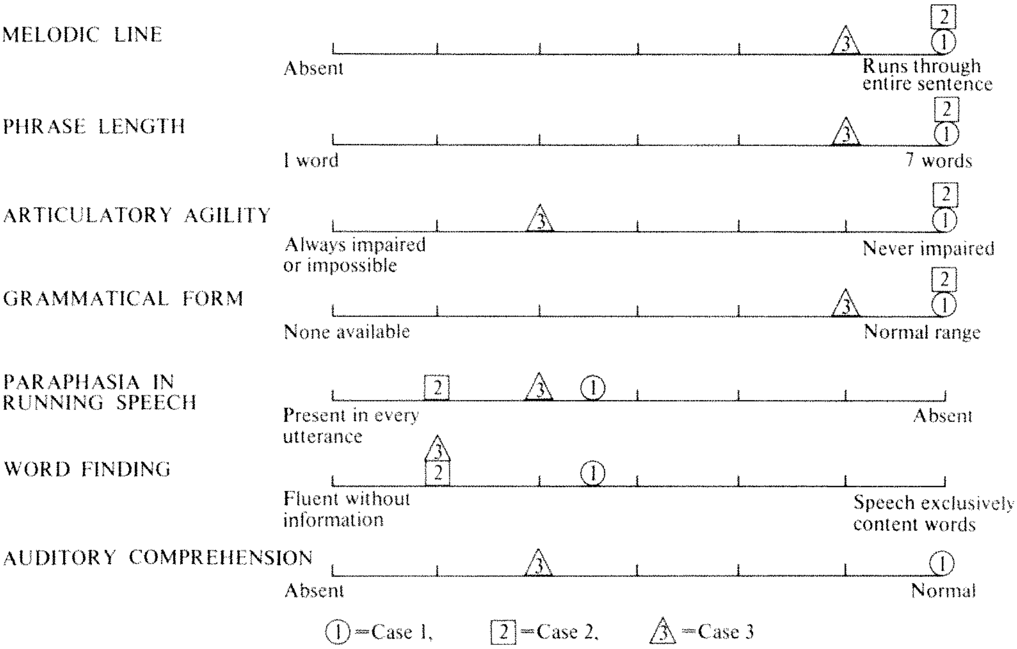

FIG. 1. BDAE speech profiles for Cases 1, 2 and 3.

Orofacial, limb and axial praxis to command and imitation were normal.

Writing posture with the right hand was noninverted (Levy and Reid, 1976). Letters were well formed, but mistakes included paragraphic errors, omissions and reiterations (fig. 2). He made more errors on phrases with few substantives. For example, the dictations *no ifs, ands or buts* and *no apples, pears or string beans* were written 'if no and and buts' and 'no apple, pears and string beans', respectively. He made errors, some due to paraphasic and paragraphic substitutions, on simple problems of oral and written arithmetic. He performed poorly when asked to name fingers or to point to individual fingers named by the examiner. On the examiner but not on himself, he confused left and right sides.

On a line bisection task (Albert, 1973), he worked from left to right, bisecting each line normally. There was no unilateral neglect, but line drawings were oversimplified. Copies were better than drawings without a model (fig. 2). He correctly identified photographs of famous faces. His scaled score on the Block Design subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1955) was 9. (The mean score for the normal reference group is 10.)

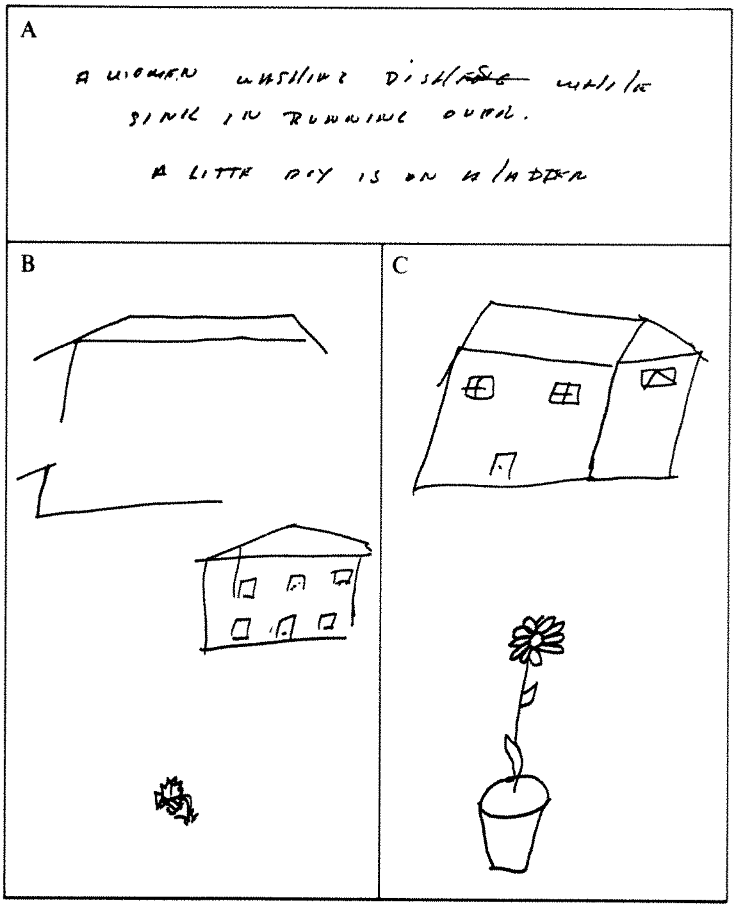

FIG. 2. *Case 1.* A, description of BDAE Cookie Theft picture. He prints 'A WOMEN WASHING DiSHING (self-corrected to DiSHES) WHIlE SINK IN RUNNING OVER. A LITTLE BOY IS ON A lATTER' (self-corrected to lADDER). B and C, drawings of a house and daisy without (B) and with (C) a model. Copies are better than his simplified drawings to command.

An electroencephalogram (EEG) showed right temporoparietal slowing. Computed tomography of the brain (CT) demonstrated two right hemisphere areas of decreased density consistent with infarcts (fig. 3). A circumscribed lesion involving the inferior parietal lobule extended from cortex to the body of the lateral ventricle. There was a smaller lesion of the head of the caudate nucleus and adjacent anterior limb of the internal capsule. The left hemisphere was normal, and CT five months later showed no new abnormality.

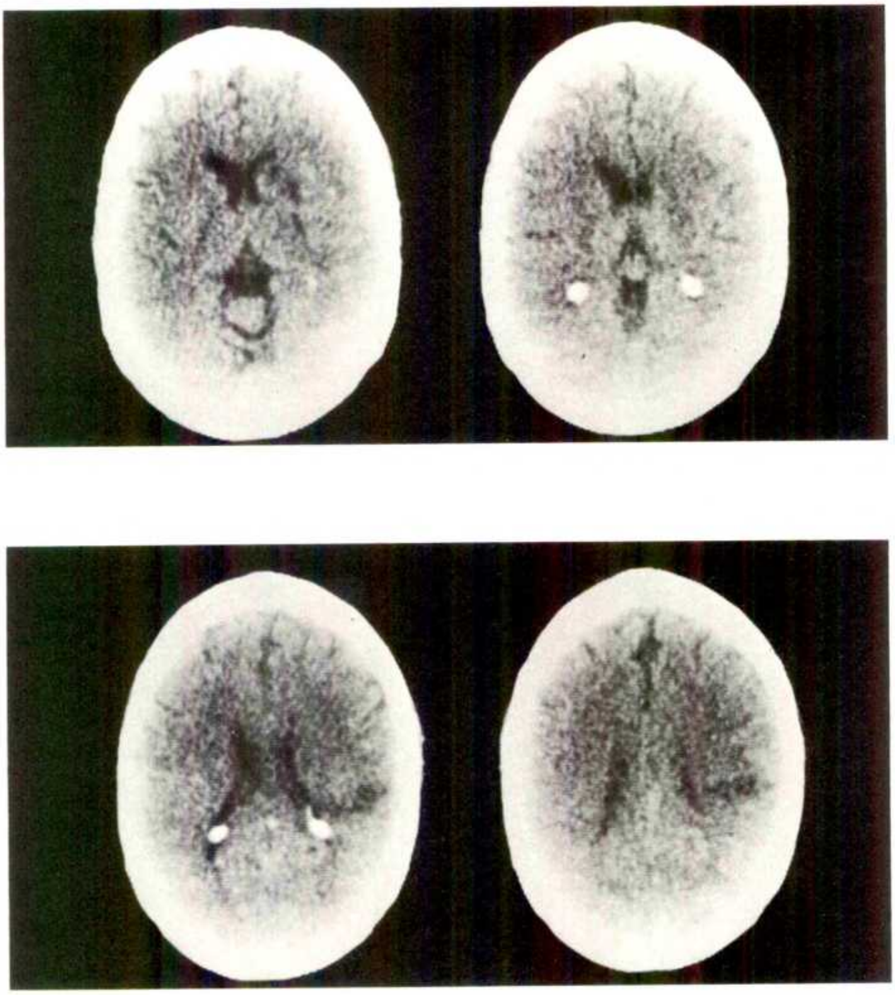

FIG. 3. CT of *Case 1*. The lower two photographs show a low-density lesion of the right inferior parietal lobule extending deeply into subcortical white matter. A smaller lesion of the head of the right caudate nucleus and adjacent anterior limb of the internal capsule is seen in the left upper CT slice.

Audiometry confirmed normal hearing within the speech frequencies. He was evaluated with dichotic pairs of one, two and three digit numbers. By reversing the stereo headphones, each pair appeared twice in reverse ear order. No instructions were given as to the order of report. He correctly named all single digits, but on 88 trials with two or three digit pairs, he made 22 unilateral errors from the right ear and 5 from the left (fig. 4).

By the time of discharge, finger gnosis and left/right discrimination had returned to normal. Rote calculations could be accurately performed, but written arithmetic remained flawed by paragraphic errors, and division was almost impossible. Auditory comprehension was completely normal, whereas speech was persistently halting with some repetition difficulty and occasional paraphasias.

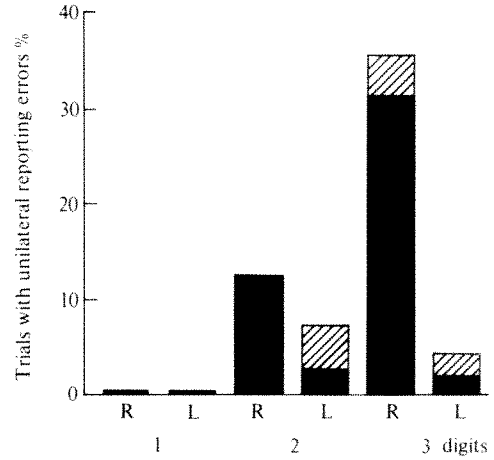

FIG. 4. *Case 1.* Unilateral errors on dichotic listening task with pairs of one, two and three digit numbers. The height of the bars represents unilateral reporting errors, while the solid portion of the bar reflects errors when order of reporting was disregarded for two and three digit numbers.

Case 2

A week before admission, a 60-year-old woman awoke with transient left-sided weakness. At another hospital, she was described as incoherent.

There was a past history of treated hypertension and chemical diabetes but no previous neurological or psychiatric symptoms. She was a high school graduate who spoke only English. She was strongly right handed (laterality quotient of 100 on the Edinburgh Inventory of handedness—Oldfield, 1971). Each of 11 first degree relatives was right handed.

She was alert but agitated and disorientated. Immediate recall was impaired. Confusion resolved gradually during her seven week hospital course. She was assessed neurologically a month after her stroke and in more detail after discharge one month later. Findings were similar, but during the earlier interview attention remained poor, press of speech with augmentation was more evident, and paraphasic errors more frequent.

She perceived hand movement in her left visual field but could not count fingers on that side or detect left-sided movement during simultaneous bilateral movements. Ocular saccades were impaired for an optokinetic target moving from her left to right. The left nasolabial fold was flattened. Strength and tendon reflexes were normal, but the left hand was clumsy. Although tactile sensation was intact, she ignored stimuli on her left limbs during bilateral simultaneous stimulation.

She was alert and orientated. The digit repetition span was five. She correctly recalled names of three items after a five minute delay. During the first interview, she was euphoric and denied any reason for being in hospital. Later, she admitted to having had a stroke but claimed full recovery.

Spontaneous speech was effortless, empty and circumloculatory with word-finding pauses. Rate was increased, and articulation, prosody and phrase length were normal. There were verbal, literal and occasional neologistic paraphasias. When asked if she recognized the name of former President Carter, she said 'That's the next another one I voted. Jorner, Jorna [the target word was *Georgia*], something around Alabama'. Automatized speech was often intact. Visual confrontation naming was impaired for object and body part names. She benefited poorly from contextual or phonetic cues. Examples of errors were 'microphone' for *magnet*, 'bullet' for *watchband*, 'jaw' for *cheek* and 'middle, that's the middle the tongue, the second hand to the tongue' for *index finger*. Repetition was normal for numbers, single words and short phrases but impaired for longer sentences. *No ifs, ands or buts* was repeated as 'no if, hamma and buts'. Auditory comprehension was intact for simple yes/no questions. Pointing to objects on command was impaired, more so when the item was identified by a functional description rather than by name. She incorrectly answered questions involving complex ideational information.

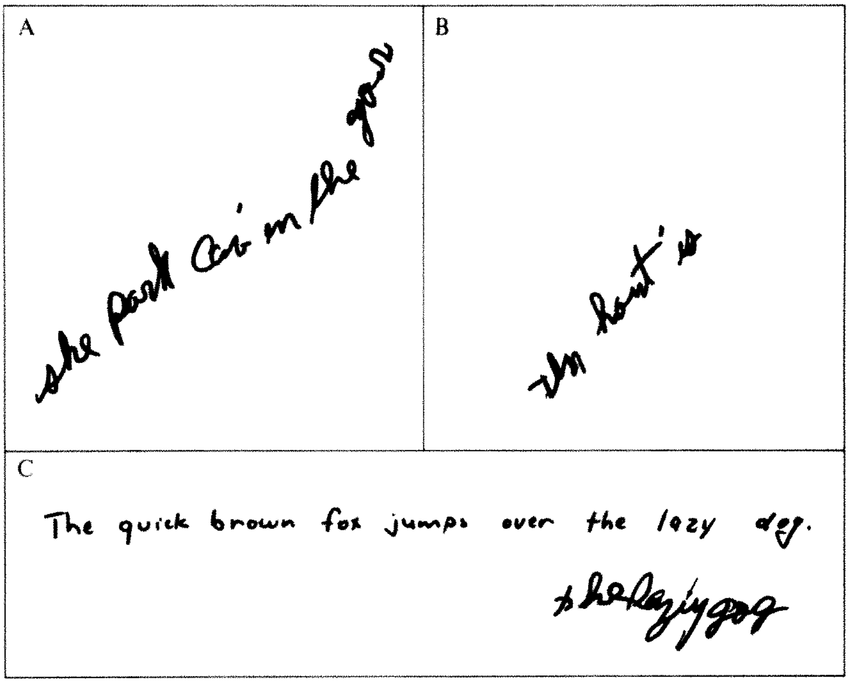

FIG. 5. *Case 2* writing samples. A, dictated as *She parked the car in the garage*. B, she was instructed to describe the weather. Asked what she had written, she said 'The weather is hot'. C, copy showing left-sided neglect. Spelling of *dog* as 'gog' and the extra stroke in *lazy* (arrow) may represent spatial dysgraphia (Hécaen and Marcie, 1974). However, linguistic errors are clearly present in other written productions.

Many oral reading errors were confined to words on the left side of the page and to the initial portion of a word. The sentences *Why did she do it* and *The airplane pilot flew over the German landscape* were read aloud as 'Did she go it?' and 'The airplane pilot went over the country and escaped', respectively. During the second interview, the BDAE aphasia severity rating was 3, and the speech profile was that of Wernicke's aphasia (Goodglass and Kaplan, 1972) (fig. 1).

Affective intonation during spontaneous speech and repetition was normal. She correctly identified affective intonation in the examiner's speech. Spontaneous facial expressions and her production of emotional expressions on command were normal. Melody while singing was good.

Orofacial and axial praxis to command were normal. On tasks of transitive limb praxis to command and imitation, she substituted a body part for intended objects (Goodglass and Kaplan, 1972).

Writing posture with the right hand was noninverted. The left margin was widened, and some lines sloped upward. Even after first correctly reading a sentence aloud, copying was impaired, although less so than writing done spontaneously or to dictation (fig. 5). She distinguished her left and right sides but not those of the examiner. Rote arithmetic calculations were accurately performed but not more complex problems. She correctly named only the thumb and little finger and consistently reversed the index and middle fingers when pointing to digits named by the examiner.

On a line bisection task, she worked from right to left, marking lines to the right of centre. Drawings to command and copy were strikingly impaired. Her approach was piecemeal (Paterson and Zangwill, 1944), she sometimes drew over the examiner's model, left-sided details were omitted, and individual features often bore little relation to the overall design (fig. 6). She identified photographs of famous faces. Her scaled score on the Block Design test was zero.

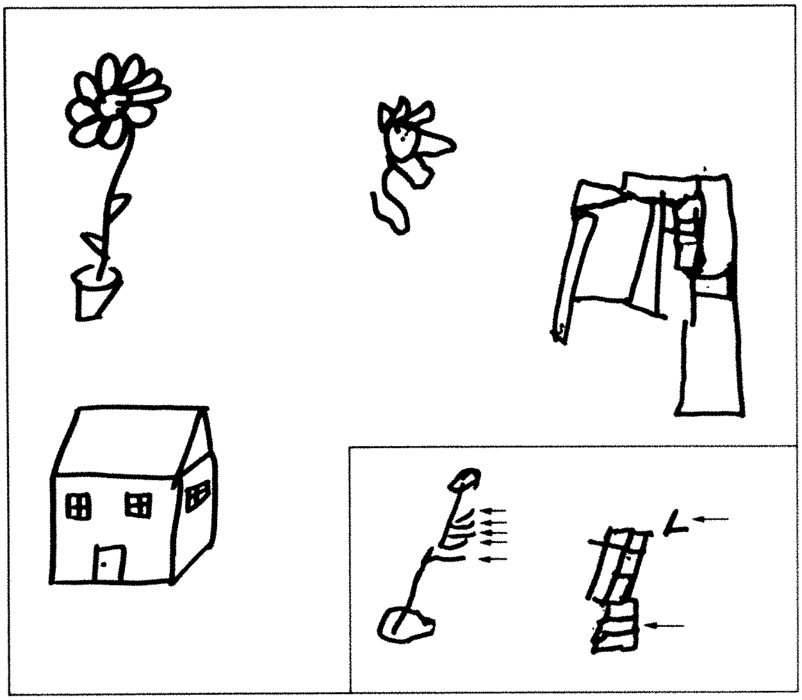

FIG. 6. *Case 2.* Drawings to command (*inset*) and copy (*models on left*). Left-sided inattention on the daisy and piecemeal approach to the house are evident. Details are placed with little regard for the overall design. Performance is not improved by the model. Arrows point to daisy petals and to the roof and stairs of her house.

Consistent with acute infarction, CT five days after onset of symptoms showed a large area of decreased density with associated mass effect, involving the right temporal, parietal and occipital lobes. Three weeks after her stroke, an EEG showed right temporoparietal delta slowing, and CT now revealed a right temporal-parietal-occipital low-density lesion without mass effect. After contrast injection, there was enhancement within this area (fig. 7).

Case 3

A 61-year-old man was admitted to hospital after the abrupt onset of left-sided weakness and language impairment. He left school in Ireland at the age of 14 but could read and write well. He spoke only English. He had been diabetic for several years. Over the past year, he had noticed a resting hand tremor, but there was no past history of other neurological symptoms. He was strongly right handed

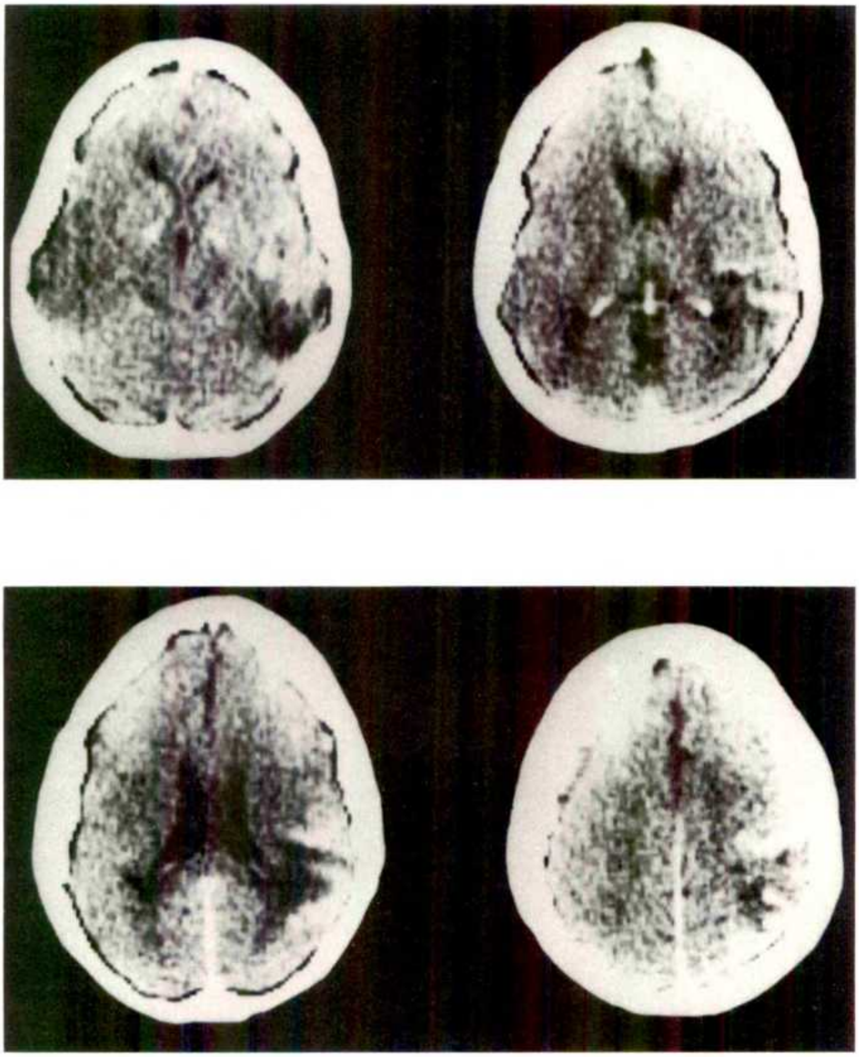

FIG. 7. *Case 2*. CT shows a contrast-enhancing right temporal-parietal-occipital infarct.

(laterality quotient of 100 on the Edinburgh Inventory of handedness—Oldfield, 1971). Each of 3 first degree relatives was right handed.

Neurological deficits were stable during evaluation two to three months after symptom onset. To confrontation there was a dense left homonymous hemianopia. Corneal sensation was depressed on the left, and pin prick was identified as less sharp on the left side of the face. He had a mild spastic left hemiparesis with brisk tendon reflexes on that side. There was an intermittent low amplitude 5 Hz distal upper limb resting tremor. Except for signs of a distal polyneuropathy, limb sensation was normal. Left-sided tactile stimuli were ignored during bilateral simultaneous stimulation.

He was alert and orientated. Affect was normal. Digit repetition span was three. He recalled names of three previously rehearsed object names after a five minute delay.

Speech was hypophonic and mildly dysarthric. Conversational speech was effortless with normal rate, prosody and phrase length. He used a variety of grammatical forms, but there were word finding pauses and he used few substantive words. There were occasional verbal, literal and neologistic paraphasias. When describing a leg injury, he said 'It was fishe o'clock they left. They table, they left the table away. Oh, it was heavy; it was heavy. As much as I could left, and then the foot sore, would, uh, the foot was, uh, feelin' well. And I skinned it and everythin'. And then they, the doctor was away on vacation, and they weren't there or nothin' '. Automatized speech was better than spontaneous speech.

Confrontation naming was impaired, more so for objects than body parts. He improved with phonetic but not contextual cues. Examples of errors were 'hand' for *glove*, 'smissor' for *feather*, 'toe' for *tongue*, 'argoni' for *elbow*, 'yellow' for *pink*, and 'like a blue, but it's not' for *purple*. Repetition was often intact at the single word and short phrase level but impaired for more complex sentences. *Shoe* was repeated as 'sugar', *under the bed* as 'under the door', *what of it* as 'what about it' and *the barn swallow captured a plump worm* as 'the barn slollowed a captured a worm'. Often correct for single yes/no questions, auditory comprehension was more consistently impaired when he responded to more complex questions or pointed to objects named by the examiner. Oral reading and his comprehension of written language were impaired. *Circle* was read aloud as 'circulet', *triangle* as 'transition', *fifteen* as 'charifant', *purple* as 'burgandy' and *The spy fled to Greece* as 'They say they to greet'. The BDAE aphasia severity rating was 2, and his speech profile was that of Wernicke's aphasia (Goodglass and Kaplan, 1972) (fig. 1).

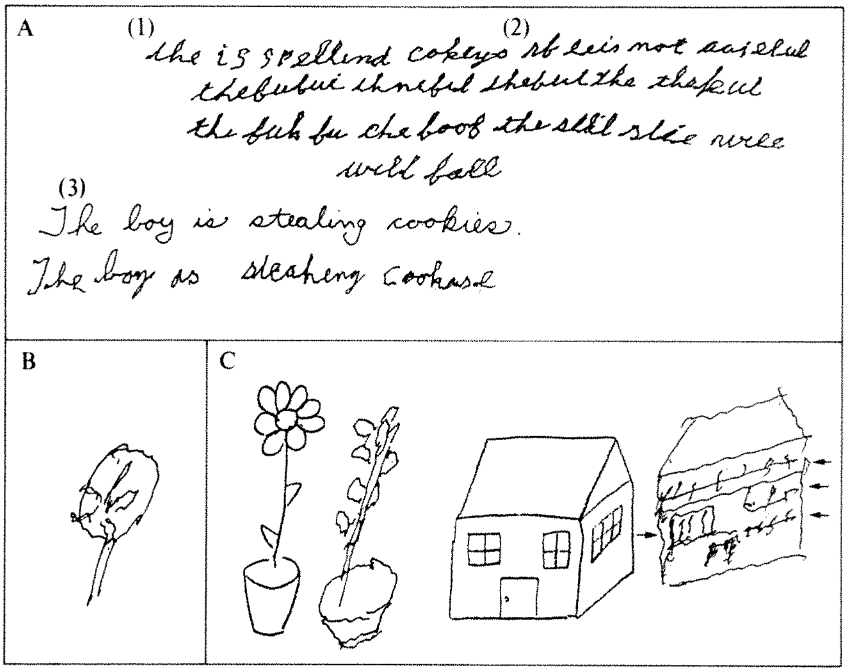
A
(1)
the is seellind cokeys
(2)
well fall
(3)
The boy is stealing cookies.
The boy as steahing cookase
B
C

FIG. 8. *Case 3.* A, writing samples. Two separately dictated sentences were (1) *The boy is stealing cookies* and (2) *If he is not careful, the stool will fall.* Particular difficulty is seen with substantive words: *boy* is omitted, *stealing cookies* is misspelled as 'seellind cokeys', and *stool* induces striking iteration. At one point, the paragraphia 'book' is written for *stool.* (3) Performance is much better when copying. B, petals of the daisy drawn to command are placed within the flower head. He would not attempt to draw a house without a model. C, copy of a daisy shows petals which extend down the stem rather than radiating from the centre. Extra windows in his copy of the house are indicated by arrows.

Affective intonation during spontaneous speech and repetition, and his ability to identify the affective content of the examiner's speech were normal, as was melody while singing. Spontaneous facial expressions, his production on command of emotional expressions and his recognition of the affective content expressed by the examiner's expressions were normal.

Orofacial and axial praxis were normal. Mild limb apraxia to command, with loss of extension and the substitution of a body part for the intended object (Goodglass and Kaplan, 1972), improved on imitation.

Writing posture of the right hand was noninverted. Handwriting was marred by tremor, and perseveration, neologisms and misspellings were common (fig. 8). He distinguished left and right sides on himself but not on the examiner. He could name only his thumb and 'wee' finger and correctly identified only the same two digits when asked to point to fingers named by the examiner. He was unable to perform simple problems of oral or written arithmetic.

On a line bisection task, he neglected lines on the left side of the page and bisected other lines to the right of centre. Line drawings to command and copy were impaired. He placed individual details without regard to the overall configuration, and the left side of some drawings was incomplete (fig. 8). He identified photographs of famous faces. His scaled score on the Block Design test was zero.

EEG showed the absence of right hemisphere alpha activity, right-sided theta slowing and occasional sharp waves from right-sided leads. CT the day of admission was normal, but one month later CT showed a nonenhancing low-density lesion involving the right inferior parietal lobule and the posterior part of the superior temporal lobe (fig. 9).

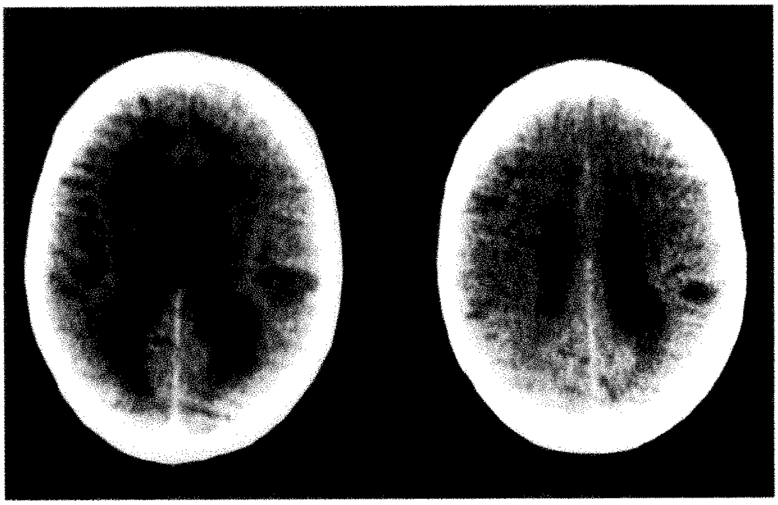

FIG. 9. *Case 3.* CT shows a low-density lesion involving the right inferior parietal lobule and the posterior superior temporal lobe.

ANALYSIS OF CASES

The accompanying neurological signs, and the EEG and CT findings suggested that aphasic symptoms in these three strongly right-handed patients were caused by right hemisphere lesions. Results of the first patient's dichotic listening task also supported this conclusion. Left parietal lesions which spare the temporal lobe usually cause a right ear advantage due in part to 'paradoxical' ipsilateral extinction of dichotic verbal material (Sparks *et al.*, 1970; Damasio and Damasio, 1979). The marked left ear advantage of Case 1 was thus predicted on the basis of his deep right parietal infarct and right hemisphere language dominance. None of these cases had a strong family history of left handedness, none had had childhood brain injury, and none was bilingual. For Cases 1 and 2, language disturbances improved somewhat over a period of several months, and for Case 3 deficits persisted.

Analysis of spontaneous speech (Benson, 1967, 1979) showed that the language disturbance in each case was fluent (*see* Table).

FLUENCY IN SPONTANEOUS SPEECH

						Word choice	
Case No.	*Effort*	*Rate*	*Phrase length*	*Prosody*	*Articulation*	*Syntax*	*Paraphasias*
1	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+
3	+	+	+	+	−	+	+

+ = features of fluent speech. Effort, rate, phrase length, prosody and articulation are normal or near normal. Syntactic word choice is normal or paragrammatic, and there are paraphasic errors. − = features of nonfluent speech. Speech is effortful, rate and phrase length decreased, and prosody and articulation abnormal. Speech is agrammatic, and paraphasias are rare.

Mild idiopathic Parkinson's disease in Case 3 is likely to have been responsible for hypophonia and dysarthria but probably did not otherwise affect speech fluency. The first patient made predominately literal paraphasic errors, but verbal paraphasias were more frequent in spontaneous speech of the second and third patients. For Case 1, comprehension was almost normal, whereas it was impaired for Cases 2 and 3. The disorders were characteristic of conduction aphasia for Case 1 and Wernicke's aphasia for Cases 2 and 3.

Conduction aphasia occurs after posterior left hemisphere perisylvian lesions which include long association fibres between posterior and frontal language areas. For a typical right-hander, conduction aphasia may follow left hemisphere injury corresponding to the first patient's cortical and subcortical infarct in the right inferior parietal lobule (Benson *et al.*, 1973; Damasio, 1981). Involving the vascular territory of the lower division of the middle cerebral artery, the characteristic lesion of Wernicke's aphasia includes the posterior left superior temporal gyrus (Wernicke's area) and surrounding regions of the temporal and parietal lobes (Mazzocchi and Vignolo, 1979; Mohr, 1980; Damasio, 1981). Sites of the second and third patients' infarcts mirrored the usual left hemisphere lesion of Wernicke's aphasia.

Cases 2 and 3 also had features of the neglect syndrome. Case 2 was unconcerned and denied the extent of her disability. Both patients ignored left-sided sensory stimuli during bilateral simultaneous stimulation. Each showed unilateral neglect on a line bisection task and in line drawings. They copied drawings no better than they drew without a model. Their approach was piecemeal, and they placed individual details without regard to the overall configuration (figs. 6 and 8). These visuoconstructive deficits are typical of those after right hemisphere damage (Paterson and Zangwill, 1944; Piercy *et al.*, 1960; Warrington *et al.*, 1966; Gainotti and Tiacci, 1970).

For several weeks after her stroke, Case 2 was confused, probably as a direct result of her right temporoparietal infarct (Mesulam *et al.*, 1976). Impaired attention is a cardinal symptom of confusion (Mesulam, 1981). Both the neglect syndrome and a transient confusional state may follow ischaemic injury to the right posterior hemisphere and have been attributed to the importance of posterior polymodal cortical association regions in mediating arousal and selective attention (Mesulam *et al.*, 1976; Mesulam, 1981). Hemispatial inattention, visuoconstructive impairments and, for Case 2, denial of illness and confusion suggest that right hemisphere dominance for attention and visuospatial functions did not differ from that of most right-handers.

In contrast, Case 1 recognized the extent and implications of his stroke. There was no inattention during bilateral stimulation. He accurately bisected lines, worked from left to right and did not ignore left-sided details when drawing. His simplified line drawings, however, were better when a model was provided for him to copy (fig. 2). This type of visuoconstructive disturbance is normally associated with left-sided injury (Piercy *et al.*, 1960; Warrington *et al.*, 1966; Gainotti and Tiacci, 1970), and right hemisphere representation of Case 1 for both linguistic and visuospatial skills seemed more typical of left hemisphere organization.

DISCUSSION

Since Dax (1865) and Broca (1863, 1865) first recognized that aphasia is caused by left hemisphere lesions, it has been known that higher cerebral functions may be asymmetrically represented within morphologically similar hemispheres. Jackson (1868), however, realized that aphasia associated with left hemiplegia might occur in some right-handers, and Bramwell (1899) later coined the term crossed aphasia (CA) to describe this seemingly anomalous discovery that language lateralization and handedness are not inexorably linked. CA has since come to refer to aphasia caused by right hemisphere lesions in right-handed persons. Its incidence is less than 1 per cent after right hemisphere lesions (Roberts, 1951; Hécaen *et al.*, 1971), and among right-handed aphasics, the prevalence of CA is also about 1 per cent (Gloning *et al.*, 1969). For left-handers, aphasia more often follows lesions of either cerebral hemisphere (Moutier, 1908; Goodglass and Quadfasel, 1954; Hécaen and Ajuriaguerra, 1964), and ambidexterity or 'ambilaterality' confounds some purported examples of CA (Kennedy, 1916; Ettlinger *et al.*, 1955).

A study of CA has implications for theories of cerebral dominance. Semmes (1968) posits that both right handedness and left hemisphere language specialization stem from focal representation of elementary sensory and motor functions, which converge at higher levels of cerebral organization to permit precise input encoding and output modulation. Diffuse or overlapping right hemisphere representation favours polymodal integration important for visuospatial perception. Since handedness and language dominance depend on a common substrate, this theory predicts that right hemisphere language representation for CA should differ from that in the left hemisphere of other strongly right-handed adults.

A similar view of CA has been more recently advanced. Several authors (Angelergues *et al.*, 1962; Brown and Hécaen, 1976; Urbain *et al.*, 1978) suggest that CA, regardless of lesion localization within the right hemisphere, is characterized by nonfluency. They argue that linguistic functions are diffusely rather than focally represented within the language-dominant right hemisphere and that lesions at any site within a diffusely organized language area cause nonfluent aphasia. These models of CA contrast to the language representation of most right-handed adults in whom anterior and posterior language regions are differentially specialized for speech production and perception. Thus, focal lesions within left hemisphere language areas cause different aphasic syndromes depending upon the specific locus of damage.

Language lateralization in CA has been directly studied twice with the intracarotid sodium amylobarbitone test of Wada (Wada and Rasmussen, 1960). For a nonfluent patient with occlusion of the right Sylvian artery, bihemispheric linguistic capacity was suggested by speech deterioration after a left carotid injection (Angelergues *et al.*, 1962). The Wada test, however, confirmed unilateral right hemisphere language dominance for Zangwill's (1979) fluent aphasic, who had a right temporal haemorrhage. Fluent language deficits for the present three patients also differed from those predicted by a model of diffuse right hemisphere language representation. Because so few cases of CA are reported, these exceptions suggest the need to reappraise this theory.

Comparison of Crossed and 'Uncrossed' Aphasia

The occurrence of aphasia does not establish a linguistic role for the injured brain area in an intact nervous system (Jackson, 1915). Nevertheless, it is reasonable to postulate that if a right hemisphere lesion impairs language differently in CA than does the mirror image left hemisphere injury in uncrossed aphasia (UCA), then language representation within the right hemisphere of crossed aphasics would differ from that usually found within the left. A conclusion that intrahemispheric language organization differs for CA is tenable only if the method of linguistic comparison between cases of CA and UCA is valid, crossed aphasics are compared with uncrossed aphasics who are otherwise similar in terms of potentially confounding variables, and lesions responsible for aphasia can be reliably localized.

Speech Fluency as a Method of Clinical Comparison

Carl Wernicke (1908) distinguished the sparse oral output of Broca's aphasia from the voluble speech and distorted use of a large lexicon of Wernicke's aphasia. A clinical classification of aphasia based on this *fluency* dichotomy is experimentally valid (Howes, 1964, 1967; Benson, 1967; Kerschensteiner *et al.*, 1972; Wagenaar *et al.*, 1975) and for classifying groups of aphasic patients is more useful than differences in language comprehension (Goodglass *et al.*, 1964; Poeck *et al.*, 1972).

Nonfluent speech is characterized by the sparse, effortful production of short phrases. Speech prosody, or 'melody', and articulation are impaired. Substantive words (nouns, verbs and adjectives) are used in preference to relational words such as articles, prepositions and conjunctions (agrammatism—Goodglass, 1976). In contrast, fluent speech is easily produced at a near normal rate. Phrase length (longest occasional uninterrupted string of words—Goodglass and Kaplan, 1972), articulation and prosody are normal, and a variety of grammatical constructions are used. There may be paraphasic errors and omissions of substantive words (Benson, 1967, 1979). Nonfluent language occurs with Broca's, transcortical motor and global aphasia; whereas Wernicke's, conduction and transcortical sensory aphasias are fluent. As inferred for UCA from the CT and the radioisotope brain scan findings, nonfluent patients have lesions centred anterior to the left central fissure, and most fluent aphasics have more posterior lesions (Benson, 1967; Mazzocchi and Vignolo, 1979; Damasio, 1981). Those with lesions of both anterior and posterior speech regions or with minor aphasic deficits such as anomia may be difficult to classify, and about one-fifth of chronic aphasics cannot be segregated into fluent and nonfluent dichotomies (Benson, 1967; Wagenaar *et al.*, 1975).

Potentially Confounding Variables

Our knowledge of left hemisphere aphasic syndromes is largely derived from observations on patients with ischaemic stroke. Infarction, unlike trauma or mass lesions, produces discrete damage amenable to clinical-anatomical correlation, and classic aphasic syndromes usually follow infarction within specific vascular territories (Boller, 1973; Mohr, 1976, 1980; Mohr *et al.*, 1978).

A large proportion of CA patients are polyglots (Marinesco *et al.*, 1938; Holmes and Sadoff, 1966; Hécaen *et al.*, 1971; Nair and Virmani, 1973; Wechsler, 1976; April and Tse, 1977; April, 1979; Zangwill, 1979; Trojanowski *et al.*, 1980), and bihemispheric language representation probably occurs more often among polyglots than monolinguals (Albert and Obler, 1978; Galloway, 1981). For each language, intrahemispheric representation is not always coextensive (Ojemann and Whitaker, 1978), linguistic functions can be selectively or differentially impaired, and recovery can be antagonistic or proceed at different rates (Pitres, 1895; Minkowski, 1963; Nair and Virmani, 1973; Paradis, 1977; Silverberg and Gordon, 1979). Although CA may be more prevalent among polyglots, bilingualism confounds extrapolation as to how linguistic functions might be organized within the right hemisphere of monolingual crossed aphasics.

Inferences concerning linguistic impairment and cerebral language organization in CA should ideally be derived from strongly right-handed monolingual adults without childhood brain damage, with adequate language testing and with discrete ischaemic lesions confined to the right hemisphere. Whether it is also necessary to control for patient age (Harasymiw *et al.*, 1981), sex (McGlone, 1977), literacy (Cameron *et al.*, 1971; Wechsler, 1976; Damasio *et al.*, 1976), handedness of relatives (Subirana, 1958), hand posture when writing (Levy and Reid, 1976) or speech therapy (Basso *et al.*, 1979) is less certain.

Localization of Lesion

Among currently available diagnostic techniques, only postmortem examination and CT provide requisite sensitivity for confident lesion localization. The radioisotope brain scan detects recent, but not older, pre-existing infarcts (Benson and Patten, 1967). Angiographic evidence of arterial occlusion is often absent in infarction, and because of variable collateral circulation, its occurence defines neither the presence nor extent of ischaemic injury (Mohr, 1976; Yarnell *et al.*, 1976).

Clinical-anatomical Correlation in CA and UCA

Among the 11 CA patients cited in support of the theory of diffuse cerebral language organization (Brown and Hécaen, 1976; Urbain *et al.*, 1978), 5 had aetiologies other than ischaemic stroke (Ettlinger *et al.*, 1955; Botez and Wertheim, 1959; Hécaen *et al.*, 1971; Brown and Wilson, 1973; Foroglou *et al.*, 1975), 8 did not have lesions localized by autopsy or CT (Ettlinger *et al.*, 1955; Botez and Wertheim, 1959; Angelergues *et al.*, 1962; Barraquer-Bordas *et al.*, 1963; Clarke and Zangwill, 1965; Hécaen *et al.*, 1971; Brown and Wilson, 1973; Foroglou *et al.*, 1975), one was ambidexterous (Ettlinger *et al.*, 1955), at least 3 were polyglots (Marinesco *et al.*, 1938; Hécaen *et al.*, 1971; Wechsler, 1976), and 2 patients had no documentation of language disturbances beyond the early period after onset of symptoms (Foroglou *et al.*, 1975; Urbain *et al.*, 1978). While there is little doubt that most of these patients did indeed have CA, inferences concerning linguistic-anatomical correlations must remain suspect.

In addition to the present 3 patients, there are only 7 cases in the world literature of strongly right-handed monolinguals without left hemisphere or childhood brain damage in whom chronic aphasia (defined as oral language deficits persisting for at least one month) followed CT or pathologically confirmed right hemisphere infarction (Lozano and Clark, 1976; Pillon *et al.*, 1979, Case 1; Yarnell, 1981, Cases 2 and 3; Denes and Caviezel, 1981; Brust *et al.*, 1982; Haaland and Miranda, 1982). As with my cases (Table), Benson's (1967, 1979) criteria were used to determine fluency from descriptions of spontaneous speech.

For anomic aphasia, deficits are too mild to permit valid correlation between fluency and site of lesion, and the CA case of Denes and Caviezel (1981) is therefore inappropriate for analysis. Three weeks after a predominantly right frontal infarct, he had a Broca's aphasia. Many acute Broca's aphasics evolve to a more fluent anomia (Goodglass *et al.*, 1964; Mohr, 1976), and six months later their patient's disturbance was that of anomic aphasia. Eight of the other 9 aphasics were fluent. For Case 1 of Pillon *et al.* (1979), fluent CA could be tentatively inferred from speech described as sparse but grammatical with verbal paraphasias, and there was clearly a fluent agraphia. The CT report of a right subcortical rolandic infarct for this patient precludes precise localization along an anterior-posterior axis. The other 7 fluent patients had documented posterior lesions. Three of these had coexisting anterior damage (Lozano and Clark, 1976; Yarnell, 1981, Case 2; my Case 1). The one nonfluent patient had infarction of the medial aspect of the right frontal lobe (Brust *et al.*, 1982).

The predominance of fluent aphasia in this series is probably an artefact related to the small number of CA cases suitable for clinical-anatomical correlation. About two-thirds of all chronic aphasics are nonfluent (Benson, 1967; Wagenaar *et al.*, 1975), and a similar proportion of nonfluent CA patients is expected if right hemisphere language organization mirrors that usually present on the left. The theory of diffuse language representation, however, would demand a yet higher nonfluency rate. Aphasia was fluent for the 2 cases in which available anatomical information was inadequate to establish location of the lesion as predominately anterior or posterior (Lozano and Clark, 1976; Pillon *et al.*, 1979) and for the case in which both anterior and posterior language regions were extensively infarcted (Yarnell, 1981, Case 2). For the remaining patients, infarct localization accurately predicted fluency based on language deficits normally seen after focal *left* hemisphere damage (Benson, 1967; Mazzocchi and Vignolo, 1979; Damasio, 1981). Thus, CA is not characterized by nonfluency, and comparably located right hemisphere lesions for CA usually cause aphasic deficits similar to those for UCA after left hemisphere lesions. These observations strongly suggest that linguistic functions within the right hemisphere of most crossed aphasics are organized like those of the left hemisphere for normal right-handed adults.

Emotional Aspects of Speech

Each of the present 3 patients conveyed appropriate affective information in his spontaneous speech, correctly mimicked affective content during speech repetition and comprehended affective intonation in the examiner's speech (Ross, 1981). These emotional components of speech are normally spared in UCA and lost after right hemisphere damage (Ross, 1981). Melody when singing, which usually depends on right hemisphere integrity (Gordon and Bogen, 1974), was also spared. Preservation of these functions implies that certain nonverbal aspects of oral communication are lateralized opposite the language-dominant hemisphere. Similar observations have not been made for other CA patients, and additional study is needed to determine whether this contralateral relation necessarily holds.

Neglect Syndrome in Crossed Aphasia

Right hemisphere lesions are often accompanied by the neglect syndrome: denial of disability, inattention to contralateral personal and extrapersonal space, and visuoconstructive impairment. Focal injury of either hemisphere causes the syndrome, but symptom severity is greater after right-sided damage (Piercy *et al.*, 1960; Mesulam, 1981). It is unlikely that selection bias accounts for the preponderance of neglect patients with right hemisphere damage. Instead, the right hemisphere is probably dominant for attentional or visuospatial functions (Piercy *et al.*, 1960; Mesulam, 1981). Findings in Case 1 and in rare reports of other right-handed patients (Brown and Wilson, 1973; Zangwill, 1979; Denes and Caviezel, 1981) imply that reversed dominance for both language and visuospatial perception skills occasionally occurs. However, constructional disturbances and hemispatial inattention are reported for other cases of CA (Marinesco *et al.*, 1938; Angelergues *et al.*, 1962; Barraquer-Bordas *et al.*, 1963; Clarke and Zangwill, 1965; Holmes and Sadoff, 1966; Kreindler *et al.*, 1966; Lozano and Clark, 1976; Assal *et al.*, 1981; Carr *et al.*, 1981; Haaland and Miranda, 1982). The neglect syndrome of Cases 2 and 3 may thus be more typical for CA, suggesting that right-sided language representation does not usually affect right hemisphere dominance for attention and visuospatial perception. These findings fail to support the general hypothesis that the type of intrahemispheric organization necessary for language specialization (Semmes, 1968) precludes dominance for attentional or visuospatial skills. Rather, cerebral specialization for these functions may occur in the same or opposite hemispheres. A basis for this seemingly independent functional segregation is unknown, and even for strongly right-handed adults, the dominant hemisphere for language or for visuospatial functions cannot always be predicted.

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CATEGORY SPECIFIC ACCESS DYSPHASIA

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SUMMARY

In this study we report our investigations of the residual auditory-verbal comprehension skills of a global dysphasic who had sustained a major left hemisphere infarction. Clinically V.E.R.'s capacity for propositional speech and her comprehension of the simplest verbal instructions appeared to be absent. Nevertheless using matching-to-sample techniques it was possible to demonstrate the selective preservation (foods, animals and flowers) and the selective impairment (objects) of specific semantic categories. Furthermore there was evidence from analyses of response consistency and presentation rate effects that her deficit was primarily one of access to the full semantic representation of words. We suggest that this access impairment arose because the system had become refractory, such refractoriness being category specific.

INTRODUCTION

Clinical neurologists have long been alert to the possibility of the selective sparing or selective impairment of a particular semantic category in spoken word comprehension, but the problem of category specificity has received relatively little attention in the experimental literature. Clinical descriptions of the selective failure to comprehend colour names and the selective impairment in the comprehension of body-part names are perhaps the most securely established instances of category specificity. But there have been other less frequently occurring and also more unexpected dissociations. For example, Nielsen (1936, p. 179) reported a patient in whom he observed a selective impairment for inanimate object names, while names of animate objects (including flower names) were relatively preserved. More recently, Yamadori and Albert (1973) described a patient who had particular difficulty comprehending words from two semantic categories, namely, colour names and *indoor* object names.

Goodglass *et al.* (1966) reported the first quantitative investigation of category specificity in word comprehension deficits. Using a multiple-choice technique they tested a series of 135 aphasic patients for comprehension of 6 verbal categories, namely, body parts, objects, actions, colours, letters and numbers. They recorded the number of individual aphasic patients who appeared to have disproportionate difficulty or disproportionate facility with a particular category. An unexpectedly high incidence of dissociations between semantic categories occured and they suggested that this may be the rule rather than the exception within an aphasic population.

On the other hand, Poeck and his colleagues emphasized word frequency as a major determinant of word comprehension rather than category specificity. Their methodology of averaging scores across groups of patients, however, minimizes the chance of observing dissociation of deficits (Poeck *et al.*, 1973). Indeed, it is the evidence of detailed single case studies which optimizes the possibility of identifying functional dissociations (*see* Shallice, 1979).

To date the experimental investigation of single cases has provided only a few instances of category specificity. The clinical observations of the selective impairment of the comprehension of body-part names have now been documented quantitatively (Dennis, 1976: McKenna and Warrington, 1978). The distinction between abstract and concrete categories of verbal concepts is known to be significant for disorders of verbal expression and for written-word comprehension deficits (*see* Goldstein, 1948; Marshall and Newcombe, 1973; Shallice and Warrington, 1975). There is some evidence to suggest that this dichotomy may be equally important for spoken-word comprehension. Warrington (1975) described a patient A.B. who had a striking deficit in the comprehension of *concrete* words as compared with abstract words, a finding which could hardly be attributed to task difficulty either in terms of conceptual understanding or ease of linguistic expression. This dissociation has now been documented in a second patient (Warrington and Shallice, in preparation). Warrington (1981) has argued strongly in favour of categorical organization of semantic systems to explain such phenomena. Although A.B.'s comprehension of concrete words was exceptionally poor, it was not observed that he had difficulty with any particular concrete taxonomic category. Evidence of more fine grained categorical organization within the semantic domain would be of considerable theoretical interest.

It is also of some interest to consider the mechanism underlying verbal comprehension deficits. It has been suggested both in the context of written-word and spoken-word comprehension deficits, that response consistency from trial to trial (or from session to session) provides some indication as to whether there is degradation of the semantic representation of a verbal concept or whether *access* to the stored information is faulty. Thus it has been held that stimulus-response consistency reflects a relatively static residual vocabulary whereas stimulus-response inconsistency reflects an accessing deficit (Coughlan and Warrington, 1981; Weigl, 1981), such that under optimal conditions or repeated testing an intact or relatively intact vocabulary would be demonstrated. A semantic access dyslexic syndrome has been described (Warrington and Shallice, 1979) but as yet a comparable deficit for spoken-word comprehension has not been reported.

A patient with a very severe global dysphasia in whom verbal comprehension appeared to be totally lost was investigated in some detail. It emerged that her residual comprehension capacities were more extensive than was clinically apparent. Our aim in this report is to demonstrate a category specific access dysphasia.

CASE REPORT

V.E.R., a 68-year-old right-handed woman, who had previously been employed as a domestic, was first admitted to the National Hospital on May 24, 1979 with a five-year history of intermittent claudication of the left leg and a two-week history of transient ischaemic episodes. Angiography demonstrated stenosis of the left internal carotid artery in the neck with occlusion of the intracavernous portion. She was transferred to St. Bartholomew's Hospital where a left-sided extra/intracranial anastomosis was performed. She was well and symptom-free until February 28, 1980 when there was gradual onset of progressive weakness of the right limbs and impairment of speech production. She was readmitted to the National Hospital on March 3, 1980 when, on examination, there was a dense right hemiparesis which affected her arm more than her leg and a severe global dysphasia. Blood flow studies demonstrated a relatively reduced flow in the territory of left middle cerebral artery. The CT scan showed a large area of low attenuation in the left frontoparietal region; there was no mass effect and the appearance was considered compatible with a recent infarction in the territory of the middle cerebral artery (*see* fig.). There was no evidence, either on clinical examination or from any of the investigations, of any right hemisphere damage.

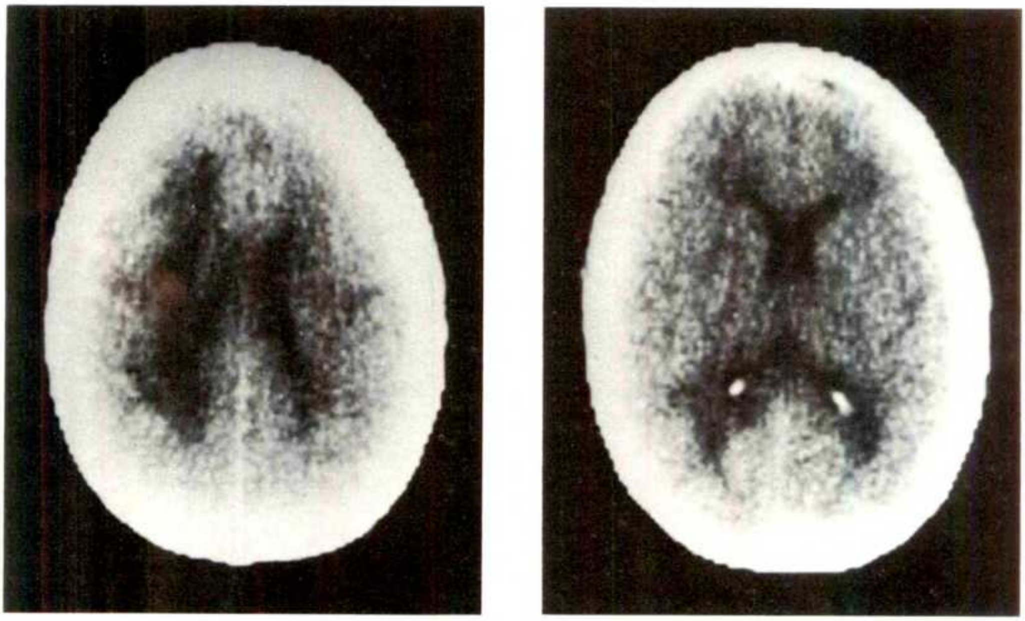

FIG. CT scan (March 7, 1980) showing a large area of infarction in the left cerebral hemisphere.

One week later, on March 12, 1980, she was seen by a clinical psychologist (P. McKenna) who noted that, although alert, V.E.R. was totally unable to produce any propositional speech and that her capacity to comprehend speech was gravely impaired; indeed there were no convincing instances of single-word or phrase comprehension. Thus she was unable to nod or shake her head appropriately to very simple questions, she could not point to her nose, point to a cup, close her eyes on request, or recognize her own name. She was totally unable to read, write or draw and she failed to score on any of the performance tests of the WAIS. Yet she was able to feed herself, to cooperate with the nursing staff in caring for herself and to cooperate in active physiotherapy. She was discharged on March 13, 1980 to

Northwick Park Hospital where she continued to receive intensive physiotherapy and, in addition, speech therapy.

Six months later, between September 25 and October 10, 1980, she was readmitted to the National Hospital for a reassessment of her neurological and cognitive deficits. On examination there was still a severe right hemiparesis affecting the arm more than the leg. Her gait had improved slightly and she was now able to walk slowly with the aid of a tripod, but there had been no improvement in the use of her right arm. Her speech production had improved slightly insofar as she would occasionally use single words, either spontaneously or in response to a question. She was now able to repeat single short words fairly accurately. She was still unable to nod or shake her head appropriately to very simple questions and she was still unable to carry out the simplest verbal instructions.

She was unable to attempt the verbal scale of the WAIS; however, 3 subtests from the performance scale were administered. She failed to score on the Block Design subtest, her responses on Picture Completion were difficult to interpret, but on Picture Arrangement she obtained an age-scaled score of 7. She appeared to be unable to comprehend the test requirements of the Progressive Matrices and testing was discontinued.

V.E.R.'s language capacities were assessed on a number of standardized tests and her performance was generally at a very low level. Her ability to name common objects and to name Objects from Description was extremely poor (1/15 and 0/15 correct). On a shortened version of the Token Test of comprehension she scored 0/15 (for a full description of these tasks, *see* Coughlan and Warrington, 1978). On the Peabody Picture Vocabulary Test (PPVT), she was unable to achieve a basal level (8 consecutive correct responses). On the first 25 items she scored only 15 items correct. Her ability to point to a named shape, colour or part of the body was very inaccurate. The PPVT was modified such that V.E.R. attempted to match the written word rather than the spoken word to the picture; again she had great difficulty and she scored only 9 correct on the first 25 items. She was unable to name individual letters or to point to a named letter reliably and she appeared to be completely dysgraphic.

In summary, six months after a major left hemisphere stroke, there appeared to have been very little improvement in V.E.R.'s language capacities. By any criterion this would be classified as a very severe global dysphasia. In particular, her ability to understand spoken speech appeared to be gravely impaired and her spoken-word comprehension deficit is the subject of the following experimental investigation.

EXPERIMENTAL INVESTIGATIONS

In this series of experiments V.E.R.'s residual auditory verbal comprehension capacities were investigated using matching-to-sample techniques. She was asked to match the stimulus item to one item of an array displayed on a desk. Each experiment was preceded by a few practice trials and the test instruction, which she appeared to understand quite quickly, was communicated by gesture. She was under no pressure to respond rapidly and self-corrections were accepted. She was tested in blocks of 20 trials throughout this series of experiments and unless otherwise stated the interblock interval was 2 min. The inter-trial intervals (presentation rate) were timed by a stopwatch from the completion of a response to the presentation of the stimulus. The test stimuli in each block of 20 trials were presented in a prearranged pseudorandom order. She was not given knowledge of results and lip reading was prevented by the experimenter sitting by her side.

Experiment 1 (October 2, 1980). Picture and Spoken-Word/Object Matching

In adopting a matching-to-sample procedure to explore *auditory* verbal comprehension, it is necessary to demonstrate that the capacity to recognize or identify the semantic connotation of the visual stimulus is unimpaired or at least relatively intact. Clinical observation suggested that V.E.R.'s comprehension deficit did not encompass her knowledge of the visual world. Nevertheless, this experiment was devised to establish that her comprehension deficit was principally in the verbal domain and not secondary to a deficit in visual recognition. Adapting a procedure first described by De Renzi *et al.* (1969), a picture/object matching task was compared with a spoken-word/object matching task. In the picture/object matching condition matching by physical attributes was minimized and matching by semantic similarity was maximized.

Procedure. The test stimuli consisted of a set of 5 objects and 5 photographs of different objects having the same name, selected so that there were 2 visually dissimilar versions of each item (for example 2 differently shaped tin openers, glasses, watches, etc.). V.E.R. was asked to match either a *spoken* name or a photograph to one of the array of 5 objects. She was tested using an ABBA design with a 2 s presentation rate. This procedure was repeated 4 times using a different set of 5 objects for each replication. There was a 4 min interval between each replication. All test stimuli were common household objects (*see* Appendix).

Results. V.E.R.'s percentage correct scores for the picture/object and spoken-word/object conditions for each of the 4 stimulus arrays are given in Table 1. For each stimulus array her performance in the picture/object matching task was significantly superior to her performance on the spoken-word/object matching task (sign test: $x = 0$, $P < 0.031$ in each replication and combining across replications: $P < 0.001$). Her performance on the spoken-word/object matching task in each replication was significantly above chance ($P < 0.05$).

TABLE 1 VISUAL AND VERBAL OBJECT MATCHING

	Auditory	*Visual*
1	47	85
2	35	68
3	43	95
4	43	100

$n = 40$. Chance = 20 per cent.

Percentage correct score for each replication on the spoken-word/object and picture/object matching tasks.

Comment. A spoken-word/object matching task demands not only the comprehension of the spoken word but also the identification of the visual object. Her very satisfactory performance on the picture/object matching task (especially on the third and fourth replications when the procedures were more familiar to her) establishes that her ability to identify visual objects—her visual semantics—were intact or very nearly so. It then follows that her deficit on the spoken-word/object matching task should be attributed to the auditory component of the task rather than the visual component and that her comprehension deficit lies principally in the auditory verbal domain.

Experiment 2. Effect of Presentation Rate on Spoken-Word/Picture Matching

It was observed that V.E.R.'s level of comprehension was strongly affected by the rate at which she was required to produce responses. On simple comprehension tasks her level of performance appeared to improve somewhat with a very slow presentation rate. Therefore the effect of stimulus presentation rate on V.E.R.'s residual comprehension skills was documented.

Procedure. V.E.R. attempted the Peabody Picture Vocabulary Test (PPVT), a 150-item graded difficulty test of receptive vocabulary, on 2 occasions. On the first (October 1, 1980), Form a was administered using a 30 s presentation rate and Form b using a 5 s presentation rate. On the second testing session (October 7, 1980) this timing was counterbalanced with Form a presented at a 5 s rate and Form b at a 30 s rate.

It should be noted that the 'fast' 5 s rate is in fact very much slower than for a normal administration of the test when there is in effect no response stimulus delay. She was tested in blocks of *25* items (not 20 as was used in the other experiments). Presentation rates were ordered in an ABBA design for test items 1 to 50. This procedure was repeated for test items 50 to 100.

Results. V.E.R.'s percentage correct score for each condition for each block of 25 trials is given in Table 2. An inspection of the table shows there was an effect of frequency ($\chi^2 = 15.6, P < 0.01$). The effect of presentation rate was also reliable (McNemar test: $\chi^2 = 12.96, P < 0.001$).

TABLE 2. PEABODY PICTURE VOCABULARY TEST

	Fast rate	*Slow rate*
Form a		
1–25	56	76
26–50	72	80
51–75	40	60
76–100	44	44
Form b		
1–25	48	64
26–50	68	76
51–75	52	80
76–100	16	28

Chance = 25 per cent.

Percentage correct score for 'blocks' of 25 items tested at a fast and slow rate.

Comment. First, this experiment has demonstrated that presentation rate can be a significant variable in V.E.R.'s auditory verbal comprehension. These findings suggest that under optimal conditions of slow presentation rate her comprehension vocabulary may be much more extensive than was apparent on clinical examination. To score 65 correct in the first 100 items of the PPVT is no mean feat for a patient who cannot respond to the very simplest of instructions. Secondly, the expected effect of word frequency was found.

Experiment 3 (October 2, 1980). Effect of Presentation Rate on Spoken-Word/Object Matching

In the previous experiment the effect of presentation rate was possibly confounded by the effects of word frequency. It was therefore considered more satisfactory to investigate the effect of presentation rate using a constant stimulus array and a design which incorporated repeated measures on the same items.

Procedure. The stimulus array for this spoken-word/object matching task consisted of the same 5 objects (torch, key, jug, saw, clip) for each condition of this experiment. There were three presentation rates, 30 s, 10 s and 2 s, which were ordered in a Latin Square design.

Results. The percentage correct for each condition is given in Table 3. The overall effect of presentation rate was significant (combined S test of trend: $J_c = 7$, $P < 0.05$). Her overall level of performance on this task was relatively poor and with the fast rate her score was not significantly above chance ($P > 0.05$). An item analysis suggested that her performance was somewhat inconsistent from trial to trial. On one item (key) she only scored 11/36 which is not significantly above chance ($P > 0.1$) but on all the other items although her overall scores were significantly above chance ($P < 0.05$) on no item was she consistently correct.

TABLE 3. PRESENTATION RATE (FIXED ARRAY)

30 s	*10 s*	*2 s*
57	52	32

n = 60. Chance = 20 per cent.

Percentage correct score on a spoken-word/object matching task at 30, 10 and 2 s.

Comment. The findings of this experiment corroborate the result of Experiment 2 and provide further evidence that it is possible to optimize conditions for her spoken-word comprehension.

Experiment 4 (October 2, 1980). Presentation Rate and Response Consistency

It has been shown that V.E.R.'s level of comprehension was affected by the presentation rate in these matching-to-sample tasks. It was also observed that her responses from trial to trial were inconsistent. Although her overall scores were significantly above chance there was not a single stimulus item to which her responses were consistently correct. This experiment was designed to obtain a measure of response consistency for a relatively large set of common object names.

Procedure. Nine different stimulus arrays of 5 objects were used for this spoken-word/object matching task. Three presentation rates, 20 s, 5 s and 2 s, were tested using a Latin Square design.

Results. The percentage correct score for each condition is given in Table 4. Her overall level of performance is somewhat better than in Experiment 3 in which the stimulus array was not changed. In this experiment the effect of presentation rate was insignificant (Jonkheere: $S = 10 = P > 0.2$).

As there were no significant effects of presentation rate in this experiment

TABLE 4 PRESENTATION RATE (VARIED ARRAY)

20 s	*5 s*	*2 s*	*Σ*
70	55	58	61

n = 60. Chance = 20 per cent.

Percentage correct score on a spoken-word/object matching task at 20, 5 and 2 s.

V.E.R.'s responses to all 45 objects were analysed for response consistency. The observed overall proportion correct could have arisen due to selective loss, or selective preservation of her knowledge of particular items. If this were so, then the majority of her responses should be either correct on every trial or mostly incorrect. The alternative possibility is that V.E.R. is equally impaired in the comprehension of all items and that her ability to produce an accurate response varies at random about a mean level of 61 per cent correct.

Her response consistency was therefore computed as follows. It was assumed that her performance on each trial for each object was independent and the binomial expansion was used to generate the expected distribution for chance variation in response consistency with $p = \text{proportion correct} = 0.61$ and $q = 1-p$. The binomial expansion yields expected proportions of responses in the categories 4, 3, 2, 1, and none correct. The expected and the observed distributions for each of these combinations are given in Table 5. Thus the observed distribution of correct responses conforms very closely to the expected binomial distribution ($S = 8$, $P = 0.05$).

TABLE 5. CONSISTENCY ANALYSIS

	Correct/incorrect response				
	✓✓✓✓	✓✓✓x	✓✓xx	✓xxx	xxxx
Expected	6.5	16.2	15.2	6.9	0.9
Observed	7	14	19	4	1

Expected and observed distribution of each combination of correct/incorrect response pattern.

In view of the significant effects of rate observed in the previous two experiments, the data from this experiment were used for a *post hoc* analysis of serial position effects. First, the slight decrement in her performance across the 20 trials (summing across 9 blocks) was not significant. However, a more fine grain analysis, considering only her first and second response to each of the 45 objects showed that the probability of responding correctly on the first trial, and incorrectly on the second trial, is significantly higher than the converse, namely, responding incorrectly on the first trial and correctly on the second trial (McNemar: $\chi^2 = 5.26$, $P < 0.05$).

Comment. It is clear from these findings (and from the observations in Experiment 3) that on tasks which V.E.R. is able to perform well above chance her performance is very inconsistent from trial to trial. The number of items on which she was consistently correct did not exceed that predicted from the binomial expansion. This same analysis effectively eliminates response perseveration as a significant factor. Since V.E.R.'s ability to comprehend varies from trial to trial this observation provides further evidence that her residual verbal comprehension vocabulary may be much greater than is clinically apparent. Possibly under optimal conditions it could be shown to be relatively spared.

Significant serial position effects would be predicted from the effects of presentation rate. At least for the first item in any block of trials the response-stimulus interval will have been 'long' or relatively long. Although no significant effects of serial position were observed across the 20-trial blocks, a reliable effect in the predicted direction was observed in her performance on the first trial compared with the second trial of each item.

Experiment 5 (October 3, 1980). Written Word Comprehension

V.E.R. appears to be totally dyslexic insofar as she failed to read aloud any words from the Schonell (1942) or Nelson and O'Connell (1978) reading tests. It was therefore of some interest to establish whether by using matching-to-sample techniques it would be possible to demonstrate, as was the case for spoken-words, a residual written-word comprehension vocabulary. Furthermore, since presentation rate was important for her spoken-word comprehension this parameter was incorporated into this experiment.

Procedure. The same 5-item stimulus array was used throughout this 2-stage experiment. For the first task the array consisted of 5 real objects and for the second task 5 written words. Thus, V.E.R. first attempted a written-word/object matching task and secondly a spoken-word/written-word matching task. V.E.R. was tested with 2 presentation rates (3 s and 5 s) using a double ABBA design for each stage of this experiment.

Results. The percentage correct score for each condition for each presentation rate is given in Table 6. On both tasks her overall level of performance is very comparable to that observed in spoken-word/object matching tasks (*see* Experiment 2). She scores significantly above chance ($P < 0.01$) with the fast rate and her score is significantly better with slow than with fast presentation for both the written-word/object and the spoken-word/written-word matching tasks. (Sign tests by items, $x = 0$, $P = 0.031$ in each case.)

TABLE 6 AUDITORY AND WRITTEN WORD COMPREHENSION

	3 s	*15 s*
Spoken-word/object	41	59
Spoken-word/written-word	44	71

n = 80. Chance = 20 per cent.

Percentage correct on the spoken-word/object and spoken-word/written word matching task at a fast and slow rate.

Comment. V.E.R.'s comprehension of written-words appears to be qualitatively similar to her comprehension of spoken-words insofar as her level of performance is affected by presentation rate. Therefore, as for the spoken-word it is not implausible to suggest that under optimal conditions it would be possible to demonstrate a much more extensive written-word vocabulary than is clinically apparent.

Experiment 6 (October 3, 1980). Abstract Word Comprehension

Spoken-word/written-word matching tasks permit the exploration of comprehension of a much wider range of verbal vocabulary than can be achieved with spoken-word/object matching tasks.

Comprehension of abstract words has not infrequently been reported to be more vulnerable than concrete word comprehension in patients with left hemisphere lesions. It was therefore of some interest to establish whether V.E.R. had any residual capacity for the comprehension of abstract words.

Procedure. The 5 stimulus item array for this spoken-word/written-word matching task consisted of 5 abstract words (good, life, work, happy, truth). V.E.R. was tested with two presentation rates (3 s and 15 s) using a double ABBA design.

Results. The percentage correct score for each condition of abstract word comprehension task is given in Table 7. With the fast presentation rate her score is at chance. However, with the slow rate she scores significantly better than chance ($P < 0.01$) and also significantly better than with the fast rate (sign test, $x = 0$, $P = 0.031$).

TABLE 7 ABSTRACT WORD MATCHING

3 s	*15 s*
19	43

n = 80. Chance = 20 per cent.

Percentage correct score on a spoken-word/written-word matching task at a fast and slow rate.

Comments. The design of this experiment does not permit a direct comparison of her capacity to comprehend concrete and abstract words. However, considering the result of this experiment, together with the findings in Experiment 6, her score on the abstract word comprehension task at a *slow* rate is very similar to her score on the concrete-word comprehension task at a *fast* rate. This observation provides very tentative evidence that her comprehension of abstract words is less efficient than of concrete words. Nevertheless, it is again not unlikely that with optimal testing conditions it would also be possible to demonstrate a relatively extensive vocabulary for abstract words.

Experiment 7 (October 10, 1980). Comprehension of Nonsense Syllables

A spoken nonsense-word/written nonsense-word matching task was devised to explore her capacity for phonological processing. In patients with an acquired dyslexia without an associated dysphasia, an almost total failure to read nonsense syllables and nonwords is frequently reported. Such observations are generally accepted as indicative of impairment of the 'phonological' reading route. While a total failure on a spoken nonsense-word/written nonsense-word matching task can be accounted for entirely by a dyslexic syndrome, some residual capacity for this task would be indirect evidence that verbal processing at the level of phonology was to some extent preserved.

Procedure. The stimulus items for this matching task consisted of an array of 3 Consonant Vowel Consonant (CVC) nonsense syllables and an array of 3 three-letter words (*see* Appendix). V.E.R. was tested (presentation rate 10 s) using an ABBA design in blocks of *18* trials (the interblock interval was 3 min).

Results. The percentage correct score for each stimulus array is given in Table 8. Her score for both nonsense syllables and words is significantly better than chance

($P < 0.02$). However, there was no significant difference between her scores for the two types of stimulus item ($\chi^2 = 0.77$).

Comment. The finding that V.E.R.'s ability to match the spoken sound to a nonsense syllable is as good as her ability to match spoken to written words indicates that her phonological reading route is not disproportionately impaired. In addition, the finding provides some very tentative and indirect evidence that the locus of V.E.R.'s deficit may not be at the level of phonological processing.

TABLE 8 NONSENSE-SYLLABLE MATCHING

Nonsense syllables	*Real words*
53	63

n = 42. Chance = 33 per cent.

Percentage correct score on a spoken-word/written-word matching task.

Experiment 8 (October 7, 1980). Phonological and Semantic Similarity

It has been demonstrated that V.E.R.'s performance is characterized by inconsistency and a decrement in performance with 'fast' presentation rates, the latter being equally the case for spoken-word and written-word comprehension. Both these factors can be considered, in some respects, in terms of 'blocking' or 'interference' phenomena. It is therefore of some interest to consider the locus of these effects. Experiment 7 provided some very tentative evidence that phonological processes were not the major determinant of her impairment. In this experiment a task was designed which permitted the direct comparison of phonological and semantic similarity in matching spoken words to objects.

Procedure. The stimulus arrays for this spoken-word/object matching task consisted of 2 objects. There were 3 conditions, semantically related object names, phonologically related object names and unrelated object names which were tested using a Latin Square design (*see* Appendix).

TABLE 9 PHONOLOGICAL AND SEMANTIC PROXIMITY

Unrelated	*Phonologically related*	*Semantically related*
70	70	57

n = 60. Chance = 50 per cent.

Percentage correct score on a spoken-word/object matching task.

Results. The percentage correct for each condition is given in Table 9. There is no decrement whatever in her performance with phonologically related object names as compared with unrelated object names. However, her score on semantically related items is at chance. Despite this floor effect there is a trend for her performance to be worse on the semantically related items ($\chi^2 = 2.7, P > 0.05$).

Comment. This result, although it does not conclusively demonstrate semantic interference effects, at least provides some evidence that V.E.R.'s comprehension deficit should not be attributed to an impairment at the level of word perception. Her performance on the phonologically related items was identical to that on the phonologically unrelated items.

Experiment 9 (October 9, 1980). Semantic Interference

This experiment was devised in order to obtain further evidence as to whether the 'locus' of V.E.R.'s deficit was within the semantic domain.

Procedure. The stimulus arrays for this spoken-word/picture matching task consisted of 2 pictures. There were two conditions, semantically related stimulus items and semantically unrelated stimulus items (*see* Appendix) which were tested using a double ABBA design.

Results. The percentage correct scores for each condition are given in Table 10. Her scores on the unrelated stimulus items were significantly higher than her scores on the semantically related items ($\chi^2 = 8.4$, $P < 0.01$).

TABLE 10 SEMANTIC PROXIMITY

Semantically related	*Semantically unrelated*
49	71

n = 80. Chance = 20 per cent.

Percentage correct score on a semantically related and unrelated spoken-word/picture matching task.

Comment. The findings of this experiment corroborate and strengthen the result of Experiment 8. A significant effect of semantic similarity would be totally inexplicable in terms of a deficit at the level of phonological processing. However, this result is entirely compatible with a comprehension deficit within the semantic domain.

Experiment 10 (October 10, 1980). Category Specificity—Object Names and Food Names

An incidental observation in a pilot study, the aim of which was to explore further the effect of semantic similarity using pictorial material, suggested that V.E.R.'s comprehension deficits might to some extent be more severe for some taxonomic categories than others. Her comprehension of food names and animal names appeared to be more intact than for object names, the category which had been used for all the previous experiments using real objects.

Procedure. In this experiment V.E.R. was asked to name and then required to repeat the name of each stimulus item both at the beginning and at the end of each block of 20 trials. The test stimuli consisted of coloured photographs of common household objects (cut out of catalogues) and of foods (cut out of recipe books). Spoken-word/picture matching using arrays of 2 and 5 object pictures and 2 and 5 food pictures was tested, using a Latin Square design (presentation rate 10 s). A different set of stimulus items was used for each array (*see* Appendix).

Results. The percentage correct for each category, for each size of array is given in Table 11. For both the 2-item arrays and the 5-item arrays there was a very significant effect of category ($\chi^2 = 6.76$, $P < 0.01$ and $\chi^2 = 18.6$, $P < 0.001$, respectively). The overall effect of size of array on her performance, computing it in terms of bits of information transmitted, was negligible. It is of some interest to note that although the capacity for propositional speech even at the level of single words was virtually absent, V.E.R.'s performance on the repetition task was very efficient. Only occasional phonemic paraphasic errors occurred. There was an insignificant trend for foods to be named more accurately than objects.

TABLE 11. CATEGORY SPECIFICITY

	Food		*Objects*	
Array size	2	5	2	5
	92	88	76	58

n = 80. Chance = 50 and 20 per cent.

Percentage correct score on a spoken-word/picture matching task (food and objects) using 2 and 5 item arrays.

Comment. The clinical impression that V.E.R. comprehended names of food better than names of objects was confirmed. All the stimulus items were familiar and there were no obvious differences between the clarity of the food and object pictures, nor on the phonological complexity of the spoken names. It seems likely that the semantic 'distance' of the food names was just as great as for the object names. It is thus reasonable to argue that there is a category specific deficity (*see below*).

Experiment 11 (October 11, 1980). Category Specificity—Objects, Flowers, Animals

It had been observed not only that there might be relative preservation of food names, but also that comprehension of animal names was to some extent spared. In this experiment a preliminary attempt to document the observation is reported. Comprehension of flower names was included in order to establish whether the observed phenomenon generalized to 'living things'.

Procedure. The test stimuli for this spoken-word/picture matching task consisted of arrays of 2-object pictures, 2-flower pictures and 2-animal pictures. The three stimulus categories were tested in a Latin Square design (presentation rate 10 s), a different set of stimulus items being used for each array (*see* Appendix).

Results. The percentage correct score for each category is given in Table 12. The overall effect of category was highly significant ($\chi^2 = 23.96$, $P < 0.001$). Her performance on the spoken-word/object matching task was just within the limits of chance ($P = 0.052$). There was no significant difference between her scores on the flower and animal categories, but both these conditions were significantly better than the object category.

TABLE 12 COMPREHENSION OF CATEGORIES

Flowers	*Animals*	*Objects*
96	86	63

n = 60. Chance = 50 per cent.

Percentage correct score on a spoken-word/picture matching task (flowers, animals, objects).

Comment. By any criterion it seems likely that the object names would be more familiar to V.E.R. than the animal and flower names. Certainly in terms of her own experience and usage the spoken-word frequency for the object names would be greater. Again it is not plausible to suggest that differences in phonological complexity or semantic similarity within the choice array could account for these findings. Although there are no appropriate ratings for guidance, *a priori* it seems more likely that the flower arrays were semantically 'closer' and possibly had the greatest potential for semantic interference effects; yet it was on this category alone that her performance was almost error-free. The findings of this experiment, together with the result of Experiment 10, suggest that V.E.R.'s auditory comprehension deficits are within the semantic domain, and further, that they are category specific.

DISCUSSION

In this series of experiments using matching-to-sample techniques we have attempted to document the residual auditory comprehension skills of a patient with a severe global dysphasia. Her very satisfactory performance on picture/object matching tasks as compared with her performance on spoken-word/object matching tasks (Experiment 1) indicates that her comprehension deficit on this task is principally within the auditory verbal domain. The nonsense-syllable experiment (Experiment 7) suggests that phonological processing was relatively intact. The absence of phonological similarity effects (Experiment 8) the occurrence of semantic similarity effects (Experiment 9) and the evidence for category specificity (Experiments 10, 11) all provide strong evidence that her deficit is within the semantic domain and would be inexplicable in terms of impaired speech perception. Further documentation of her comprehension deficit indicated that her performance on a variety of verbal-visual matching tasks was characterized by response inconsistency and strongly affected by presentation rate. Two issues merit further discussion: the theoretical significance of her category specific impairment and the mechanisms underlying her verbal comprehension deficits.

We have found very clear evidence for category specificity. Object names were comprehended significantly less well than flower or animal names (Experiment 11). In this experiment only 6 items from each category were tested and it may be objected that this finding was due to an item selection artefact which would not generalize to other instances of those categories. However, this argument cannot so easily be applied to the finding that performance on the food name comprehension task was significantly better than the comparable object name task (Experiment 10). In this experiment a total of 28 instances from each category was tested. Furthermore, we would argue that these findings cannot be accounted for in terms of task difficulty. First, the stimulus items selected for these experiments were well matched for frequency (Appendix). Secondly, in terms of her own experience, common household objects are likely to have been more familiar than the flowers and animals. Thirdly, semantic 'distance', which was shown to be a significant variable as it is for normal subjects (*see* Rips *et al.*, 1973), is likely to be at least as great for objects as for animals and possibly greater than for the flowers and foods. Lastly, and perhaps more compelling, is that the converse dissociation has also been observed, namely, the relative preservation of object name comprehension as compared with living things and food names (Warrington, 1981; Warrington and Shallice, in preparation).

The organization of semantic memory systems has most often been conceptualized in terms of either associative networks or hierarchical structures. Neuropsychological evidence suggests that a complex hierarchical process may be the more appropriate model (e.g. Warrington, 1975; Goodglass and Baker, 1976). One phenomenon has been described which would appear difficult to explain by any other model. First, the attainment of a full semantic specification of a verbal concept appears not to be an all or none step that implicates a simple S–R link, but rather a complex process. In children acquiring word meanings (*see* Clark, 1975) and in adults (*see* Putnam, 1975) there appears not to be a complete semantic representation for concepts at the limit of the individuals' verbal knowledge. The processes mediating word meaning can be partially disrupted. Further the degree of specificity is ordered such that the differentiation of 'close' concepts presupposes differentiation of 'distant' concepts in the hierarchy but *not vice versa*. Thus entry to a hierarchy is *via* the superordinate and by progressive differentiation a concept is distinguished by the attributes and associations which uniquely specify it. The vulnerability of subordinate categories as compared with superordinate categories is well documented not only in patients with spoken-word comprehension deficits but also in patients with written-word comprehension deficits.

The category specificity of V.E.R.'s comprehension deficit provides further evidence to support a hierarchical process. The selective impairment of object names together with the relative preservation of food names would be very difficult to incorporate into any form of associative network. For example, bottle and milk or bread and knife could be considered 'close' in an associative network but have been shown to be very 'distant' in the categorical organization observed in V.E.R.

We would infer not only that the neurological substrates subserving differentiation within these categories differ, but also that the relevant processes which permit access to the appropriate semantic representations are required to be different. We would therefore tentatively suggest one possible explanation for the necessity of separate mechanisms to achieve full semantic specification.

Consider differentiating between two types of item: a wallet and a purse as compared with a cabbage and a cauliflower. In the first case, sensory attributes are relatively unimportant (wallets can be of very different shapes, colours and sizes) whereas in the second it is these very sensory attributes which are crucial. On the other hand, functional attributes would appear to be of less importance in discriminating between a cabbage and a cauliflower but essential in differentiating a wallet from a purse. We would speculate that this formulation may have general applicability; artefacts are predominantly defined in terms of their usage whereas items in the other categories which we have tested are discriminated mostly in terms of their sensory features. It seems not implausible to suggest that a cognitive structure which subserves tighter and tighter functional differentiation is likely to have different properties than one which is based on sensory features.

This is no more than a *post hoc* rationale, attempting to account for unexpected dissociations observed in the residual comprehension skills of a single case. It will be important to establish in further cases whether the suggested distinction between functional and sensory attributes is valid. If not, it may be necessary to consider the possibility of an even more fine grained categorical organization of the verbal semantic systems than has hitherto been supposed. However, such a distinction has in fact already been explored in studies of the acquisition of word meanings (Nelson, 1973) and discussed theoretically in the context of adult word comprehension (Miller and Johnson-Laird, 1976). Our formulation will inevitably be an oversimplification. For example, it would be premature to attempt to relate the present findings to such issues as multiple representation in the lexical thesaurus or the processes allowing interrelationship of these categories.

If we accept that V.E.R. has a category specific verbal comprehension deficit, the question arises as to whether this is a consequence of degradation within her verbal semantic system or whether the central representation is relatively intact but access to it is faulty. It has previously been argued that response consistency and response inconsistency provide an index of these two facets of impaired comprehension. A fixed or deteriorating knowledge base will be more likely to give rise to consistent patterns of response, whereas access deficit will result in an inconsistent response pattern (Warrington and Shallice, 1979; Coughlan and Warrington, 1981).

V.E.R.'s performance was characterized by temporary inability to respond accurately. This was documented both in the effects of presentation rate and in an analysis of her error patterns. By optimizing test conditions with long intertrial intervals her comprehension vocabulary was considerably larger than standard clinical testing suggested. Thus, both the error analysis and the effects of presentation rate suggest that her difficulties arise from an inability to access stored information efficiently.

Although presentation rates can be a significant factor for comprehension in aphasic patients (*see* Gardner *et al.*, 1975; Santo Pietro and Rigrodsky, 1982), the effects of intertrial interval have not been documented previously in a patient in whom a semantic *access* deficit has been identified. Following the conceptualization of Luria (1976) we would suggest that the system mediating access to V.E.R.'s verbal semantic knowledge base becomes *refractory*. Whether a refractory system is best viewed as an unstable one with an increase in the signal/noise ratio or whether the system itself becomes temporarily inactive is uncertain, and too speculative an issue to elaborate here. In purely operational terms the outcome would be similar, namely, a reduction in the ability to utilize the system efficiently for a period of time following activation.

The concept of refractoriness provides a basis for interpreting a wide range of empirical observations. First, response inconsistency is clearly interpretable in these terms for, if the system were refractory, accuracy would be reduced until such time as the system had returned to its baseline state. Secondly, the observation that there was only a decrement between the first and second trial on an item, and not a serial position effect across all trials, is explicable in terms of a refractory process reaching asymptote after a single activating event. Thirdly, intertrial interval effects are also interpretable in terms of this concept, and provide an index of the rate at which the system recovers from such activation.

Lastly, the concept of a refractory phase also helps resolve the seeming contradiction that access deficits that are *not* stimulus specific can nevertheless be category specific. We would infer that there was relative independence of the operations involved in accessing particular semantic categories. Thus if only the 'object' category were refractory, an access deficit would be observed for items in that category but not necessarily for nonrefractory categories (for example, 'food'). The effects of semantic proximity can also be understood in these terms by assuming a gradation of refractoriness within a semantic category. It therefore follows that items that are close in semantic space will be less accessible than those that are more distant during the refractory phase.

We have suggested two concepts to account for the characteristics of V.E.R.'s comprehension deficit. First, category specificity accounts for the dissociations we have observed in her abilities and inabilities to comprehend verbal categories. Secondly, an access dysphasia accounts for the temporary unavailability of verbal semantic information. These concepts may have greater generality; it seems plausible to suggest that similar phenomena may be observed in a variety of dysphasic syndromes. An obvious parallel is the nominal dysphasic in whom responses are typically inconsistent and whose misnamings are frequently close semantic approximations.

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APPENDIX

Experiment 1

Set 1 Clip, Bulb, Sharpener, Shoe, Glass
2 Clock, Jug, Key, Can Opener, Squeezer
3 Goggles, Purse, Saw, Leaf, Curler
4 Bottle, Brush, Spanner, Plug, Torch

Experiment 4

Array 1 Knife, Lock, Pen, Soap, Glove
2 Plant, Bottle, Doll, Comb, Envelope
3 Jar, Bell, Toothbrush, Pencil, Lipstick
4 Lampshade, Spoon, Teabag, Glasses, Cigarette
5 Slipper, Fork, String, Coin, Book
6 Jumper, Ring, Cotton, Plug, Saucer
7 Rubber, Thermos, Ruler, Belt, Brush
8 Teacloth, Wool, Ball, Nail-file, Shell
9 Sponge, Lid, Apple, Peg, Ashtray

Experiment 7

Nonsense syllables	MEP, TOU, KAL
Real words	MEN, TEA, CAT

Experiment 8

1. Unrelated words	Soap–Bulb, Ball–Slipper, Nail–Tissue
2 Semantically related words	Matches–Cigarettes, Glove–Scarf, Knife–Spoon
3. Phonologically related words	Bat–Hat, Ring–String, Shell–Bell

Experiment 9

Semantically related	*Semantically nonrelated*
1. Torch–Bulb	1. Purse–Doll
2. Sponge–Soap	2. Ring–Bat
3. Watch–Clock	3. Rubber–Cup
4. Brush–Comb	4. Ball–Jar

Experiment 10

Food arrays of 2
1. Carrots, Biscuits
2. Rolls, Lettuce
3 Onion, Grapefruit
4 Jam, Sprouts

Food arrays of 5
1. Soup, Ham, Bun, Shrimp, Grapes
2. Chicken, Orange, Rhubarb, Icecream, Mushroom
3. Apples, Leeks, Cake, Steak, Rice
4 Pineapple, Cucumber, Toast, Fish, Potato

Object arrays of 2
1 Towel, Slippers
2 Axe, Pram
3. Fork, Nails
4. Spoon, Piano

Object arrays of 5
1. Scissors, Wallet, Stool, Hammer, Hoover
2 Blouse, Thimble, Kettle, Thermos, Dustbin
3 Torch, Pen, Clock, Brush, Jar
4 Drill, Phone, Typewriter, Guitar, Sink

Experiment 11

Flowers
1 Rose, Crocus
2. Thistle, Daffodil
3 Carnation, Buttercup

Animals
1. Peacock, Duck
2 Stag, Giraffe
3. Ladybird, Wasp

Objects
1. Scissors, Hammer
2. Umbrella, Briefcase
3. Mop, Steps

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PHYSIOLOGICAL DEFICITS IN THE VISUAL SYSTEM OF MICE INFECTED WITH SEMLIKI FOREST VIRUS AND THEIR CORRELATION WITH THOSE SEEN IN PATIENTS WITH DEMYELINATING DISEASE

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SUMMARY

Electrophysiological recordings were made from the superior colliculus of mice infected with Semliki Forest virus (SFV) which produced patchy demyelination in many different locations within the central nervous system including the optic nerve. Over a wide range of light intensities, the visual latencies of both single cell and field potential responses from the superior colliculi of infected mice were longer than those of the corresponding control mice, and there was a greater interocular difference in visual latency in the infected mice than in control mice. In addition, the collicular neurons of infected mice revealed a loss of sensitivity to light of approximately 0.5 log units and a significant reduction in flicker fusion frequency. Using the same flash stimuli as in the mouse experiments, visual evoked potentials (VEPs) were recorded from patients with demyelinating disease. Patients diagnosed as suffering from multiple sclerosis showed a clear increase in peak latency of the VEP and a significantly reduced VEP flicker fusion frequency, as found in the SFV infected mice. These results suggest that mice infected with SFV may provide a suitable animal model of demyelinating disease.

INTRODUCTION

The theory that multiple sclerosis may be a virus-induced disease is still debated, but remains a plausible hypothesis (*see* Johnson, 1975; Fraser, 1977; Meulen, 1978). In view of a mildly hyperactive immunological response towards measles virus found in patients with multiple sclerosis (Adams and Imagawa, 1962; Brody *et al.*, 1972; Haire, 1977) and the finding that Semliki Forest virus has similarities to measles virus (Andrewes *et al.*, 1978), the demyelinating condition caused by Semliki Forest virus (SFV) is a particularly suitable animal model for studying the underlying mechanisms of demyelinating diseases in man. Indeed, avirulent SFV infection in Swiss A^2G mice has been shown to cause patchy demyelination in the cerebellum and medulla (Chew-Lim *et al.*, 1977; Suckling *et al.*, 1978) and in the optic nerve (Illavia *et al.*, 1982). On the basis of a controlled anatomical study in which normal and infected optic nerves were paired, embedded, cut and stained together (Fleming *et al.*, 1982), SFV infection was found to produce demyelination in the optic nerve fibres of all infected mice investigated at six to fourteen days after inoculation at 4 and 6 weeks. A microdensitometry study carried out in ten paired optic nerves (Fleming *et al.*, 1982) showed that the extent of demyelination varied from mouse to mouse, ranging from about 10 per cent to as much as 90 per cent of all fibres.

Physiologically, demyelination in the nervous system causes slowing and eventual blocking of conduction in myelinated nerve fibres. This has been demonstrated in demyelination caused by, for example, acute damage to the myelin sheath by diphtheria toxin (McDonald, 1963; Bostock *et al.*, 1978) or chronic demyelination produced by experimental allergic neuritis and encephalomyelitis (Hall, 1967; Kraft, 1975; Hayreh *et al.*, 1981; Tuck *et al.*, 1981). No previous studies are available, however, to answer the question whether or not virus-induced patchy demyelination can cause similar physiological deficits to those found in patients with multiple sclerosis. It is of considerable interest, therefore, to study optic nerve function in mice infected with SFV by physiological techniques which are analogous to those applicable to the study of optic nerve function in man.

Since we already knew the extent and degree of demyelination quantitatively (Fleming *et al.*, 1982), our immediate problem was whether or not such physiological techniques could detect physiological deficits in demyelinated optic nerve fibres similar to those found in clinical cases of multiple sclerosis. To investigate the physiological deficits, electrophysiological recordings were made from the superior colliculus which is the largest structure in the mouse visual pathway that receives a direct input from the optic nerve. To compare the extent of the visual deficit in the mice with virus-induced demyelination with that in patients with multiple sclerosis, the visual evoked responses of these patients were recorded using the same visual stimuli as for the mice.

METHODS

Studies in Mice

Both sexes of the St Thomas' Hospital Medical School strain of albino mice, originally bred from Swiss A^2G mice, weighing 18 to 45 g were used. Twenty-one mice were used as controls; they received 0.1 ml of bovine albumin phosphate saline (BAPS) intraperitoneally at 4 and 6 weeks of age. Thirty-five other mice received an intraperitoneal injection of 0.1 ml avirulent Semliki Forest virus (SFV) in BAPS at 4 and 6 weeks of age. The viability of the virus was checked at the time of inoculation by inoculating 3- to 4-day old baby mice intracerebrally with 0.02 ml SFV in BAPS. Only the virus which caused the death of the baby mice within two to three days was used. The viral inoculation was given twice, as this had been shown to produce greater demyelination in the cerebellum and medulla by Chew-Lim *et al.* (1977).

By simply observing the behaviour of the mice in the cage, it was impossible to distinguish the mice infected with SFV from the control mice, although an impression was gained that the SFV infected mice groomed more often than the control mice after inoculation. Approximately 10 per cent of SFV infected mice (4 out of 35 mice) showed some degree of paralysis of one or both hind limbs.

Electrophysiological recordings. Electrophysiological recordings were made between four and fifteen days after the second inoculation. The mice were anaesthetized with 60 mg/kg pentobarbitone sodium (Sagatal, May and Baker), and 2 mg prednisolone (Deltastab, Boots) for the initial surgical preparation. The operation consisted of a tracheostomy and craniotomy over the superior colliculus.

The dura was left intact. The mouse was then placed in a stereotaxic head holder (built by Mr J. Osborne, Physiology Department, University College, London). The body temperature of the mouse was maintained at 37.0 to 37.5° C using a thermostatically-controlled blanket. The electrocardiogram was monitored throughout and recordings were performed in mice with heart rates between 480/min and 720/min. During the electrophysiological recordings from the superior colliculus, anaesthesia was maintained by additional doses of pentobarbitone (0.02 mg doses) intraperitoneally and subcutaneous chlorpromazine (0.12 mg doses). The craniotomy was protected by a well of agar.

Two types of electrical recording were undertaken: recordings fron single nerve cells in the superior colliculus and recordings of field potentials. The recordings from a single cell were performed, using glass-coated tungsten microelectrodes (Merrill and Ainsworth, 1972) at 0.5 to 1.0 mm laterally and 0 to 1.0 mm anteriorly from the point where the lateral and medial sinuses meet and at a depth 750 to 1000 μm. To record field potentials, an electrolytically sharpened tungsten needle, varnished to within approximately 100 μm of the tip, was used at the same coordinates. The recording technique for spike activity and for field potentials was conventional. The frequency band width of the amplifier was 80 Hz to 30 kHz for the single cell recordings and 0.2 to 200 Hz for the field potential recordings.

Visual stimulation. The eyes were dilated by instillation of atropine sulphate and kept moist by continual application of saline from a Pasteur pipette. The mouse faced a tangent translucent screen 28.5 cm from the eye which covered the whole of the visual field of the contralateral eye. Since about 97 per cent of the optic nerve fibres decussate in the mouse, only the eye contralateral to the superior colliculus from which the recording was made was stimulated, although the superior colliculi on both sides were investigated in each mouse whenever possible.

For single cell recording, briefly flashed spots were back projected on to the screen using a strobe flash (Digitimer photic stimulator 3182). The intensity of the spot could be varied in half log unit steps using neutral density filters. The maximum intensity achieved was approximately 3.5×10^4 cd/m^2 determined by an SEI photometer and the level of the background screen illumination was approximately 1.0 cd/m^2.

The size of the spot could be varied from 5 to 20 deg. By varying the position of the spot and its size, the optimal spot size and the receptive field were determined. For the field potential recording, the strobe flash with a diffuser was placed so that it covered 100 deg of the visual field of the eye. The maximum intensity used for recording the field potential was thus approximately 5×10^5 cd/m^2 at the eye. For both single cell and field potential recordings, the rate of flash of the stimulus was varied from 1 to 30 Hz.

Analysis of responses. Single cell spike activity was analysed by constructing poststimulus histograms (PSTH) using a Biomac 1000 averager for each stimulating condition and the visual latency of the cell was measured using PSTHs with a high temporal resolution as described by Ikeda and Wright (1975) for single cell analysis in the visual cortex of the cat.

Field potentials from the superior colliculus were recorded and averaged using a technique similar to that used for recording visual evoked potentials in man. Responses were averaged and plotted on an X-Y recorder. The amplitude and timing of the responses were measured later. All statistical analyses were carried out using a PET computer (Commodore CBM 4016).

Studies in Patients

Visual evoked potentials (VEPs) were recorded from 71 patients referred to our clinic with suspected multiple sclerosis. The method of recording pattern VEPs has been detailed elsewhere (Ikeda *et al.*, 1978). For flash VEPs the response was recorded between midoccipital (5 cm above the inion) and midfrontal reference electrodes. The contact resistances of the electrodes were maintained at 1.5 KΩ or less in every patient. The patient sat facing a strobe flash (Digitimer photic stimulator 3182) subtending approximately 50 deg at the eye. The frequency of flash could be varied from 1 to 30 Hz. The maximum intensity of the flash was similar to that used for field potential recording in mice.

The potential recorded was amplified and averaged using a Medelec DAV6 averager (bandwidth of amplifier, 0.32 to 800 Hz). Each eye was tested separately. Routinely 100 to 200 responses of 1 or 4 Hz flash VEPs were averaged and the peak latency and amplitude of the major positive wave were measured in the same way as the pattern VEPs. For flicker VEPs to flashing rates greater than 15 Hz, a sweep period of 500 ms was used so that flicker wavelets could be visualized and the wavelets' amplitudes could be measured. Again, 100 to 200 sweeps were averaged.

RESULTS

Studies in Mice

Single units study. A total of 455 single units were recorded from the superficial layers of the superior colliculus where the retinal fibres terminate. Of these, 160 cells were from 9 control mice and 295 cells from 18 SFV infected mice. The recordings were carried out between four and fifteen days after the second inoculation of either BAPS (control) or SFV in BAPS (infected) at 6 weeks of age. Thus, the age of the mice at the time of recording ranged from 46 to 57 days.

Field potentials study. The collicular field potentials were also recorded at 23 penetration sites in 12 control and at 44 penetration sites in 17 SFV infected mice at the same period after the second inoculation.

The response latency of collicular cells to optimal visual stimuli (*visual latency*). Fig. 1A illustrates poststimulus histograms obtained from a collicular cell in a control mouse (age 48 days) and from a collicular cell in an infected mouse (age 46 days), which showed hind limb paralysis. The cells were responding to an optimal spot located at the receptive field centre, and flashed at 1 Hz. Poststimulus histograms such as this were used to determine the latency of collicular cells to a visual stimulus. For both cells the optimal spot was 20 deg and both had a receptive field in the inferior temporal quadrant of the visual field. The visual latency (time from the stimulus 'on' to the start of the sharp rise in the response) for the cell from the control mouse was 23 ms, whereas that for the cell from the SFV infected mouse was 51 ms.

Fig. 1B compares the field potential obtained from the surface of the superior colliculus of a control mouse (age 53 days) with that obtained from an infected mouse (age 47 days). The visual latency of the field potentials was determined by a method similar to that used for recording visual evoked potentials from patients (Halliday *et al.*, 1976), that is, measurement was made between the onset of stimulation and the first major positive peak. Thus, in fig. 1B the visual latency for the control response was 29 ms, whereas that for the response from the SFV infected mouse was 53 ms.

The visual latencies of both the single cell and the field potential responses from the superior colliculi of the infected mice were longer than those of the corresponding control mice. In addition, both the firing patterns of the single cell response and the field potential waveform obtained from the control mice were sharply peaked in contrast to those from the infected mice.

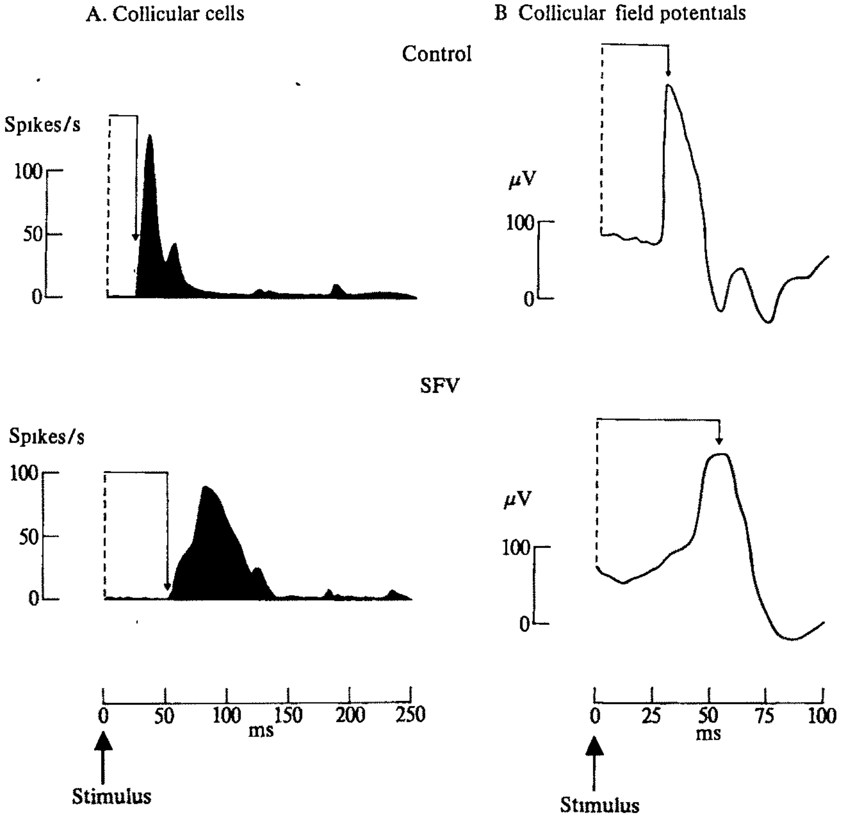

FIG. 1. A, method of visual latency measurement using poststimulus histograms of cell responses. Each histogram was constructed over 32 sweeps. In each case, the stimulus was an optimal spot flashed at 1 Hz and with optimal intensity at the receptive field centre. The receptive field centre for both control (*top*) and SFV (*bottom*) cells was in the inferior nasal quadrant of the visual field. The arrows indicate how visual latency was measured. The bin width of the histograms was 2.5 ms. B, method of visual latency measurement using averaged field potentials recorded from the superior colliculus of a control mouse (*top*) and a mouse infected with SFV (*bottom*). Each trace is the average of 64 sweeps. In each case the stimulus was a diffuse flash covering 100 deg of the visual field of the eye, flashed at optimal intensity at 2 Hz. The bin width of the histograms was 1.25 ms.

The visual latencies of the single units were a few milliseconds faster than the peak latencies of the field potentials (*see also* fig. 2). In some mice, both single units and field potential recordings were carried out: there was then a close correlation between the visual latencies of the single units and the peak latencies of the field potentials. Those mice which showed a greater delay in the single unit firing always showed a greater delay in the field potential peak.

Fig. 2A shows visual latency histograms obtained from such responses as those illustrated in fig. 1A. Data from both the left and right superior colliculi have been combined. The latencies to an optimal visual stimulus ranged from 19 ms to 32 ms in the control mice (9 mice, 160 cells). The latencies of the superior collicular neurons in the SFV infected mice (18 mice, 295 cells) were, on the other hand, much more

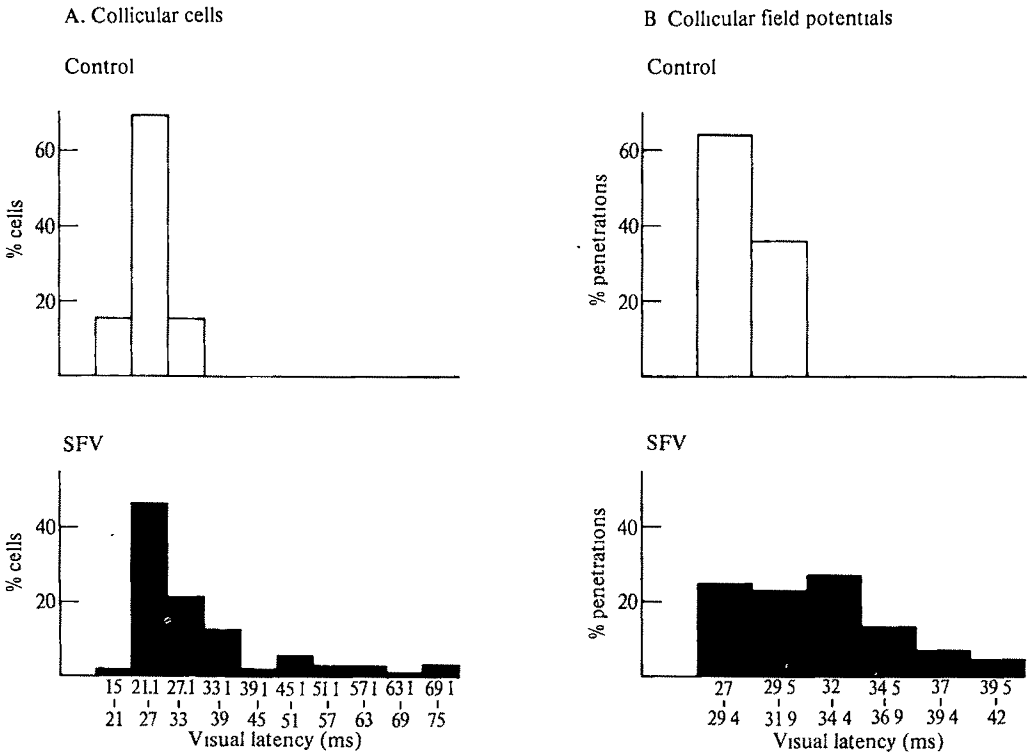

FIG. 2. Visual latency histograms for collicular cells (A) and collicular field potentials (B). The histograms show the percentage of collicular cells or field potential penetrations with visual latencies in the range shown on the abscissa. Each visual latency was the fastest latency obtained with a spot of optimal size and intensity flashed at 1 Hz at the receptive field centre, for the collicular cells, or with a diffuse flash covering 100 deg of the visual field and flashed at 2 Hz, for the field potentials.

widely spread. Although approximately 70 per cent of collicular cells still had normal visual latencies, the histogram is skewed considerably to the right and about 30 per cent of cells recorded from the infected mice had latencies beyond the normal range. It was noted that most of these cells which had considerably longer latencies were obtained from mice at eighteen to twenty days after the first SFV inoculation. The mean latency for the control cells was 24.2 ms ± 0.2 SE, while the mean latency for the SFV cells was 30.0 ms ± 0.6 SE. The difference was significant ($P < 0.001$).

The data shown in fig. 2B combine results obtained from the left and right superior colliculi, that is, those obtained from left and right eye stimulation, for all field potential penetrations recorded in control mice (12 mice, 23 penetrations) and in SFV infected mice (17 mice, 44 penetrations). The mean peak latency for the field potentials in the control mice was 29.4 ms ± 0.3 SE, whereas that in the SFV infected mice was 32.3 ms ± 0.5 SE (difference significant $P < 0.001$). Thus, the mean collicular field potential latency was significantly longer in SFV infected mice than in control mice.

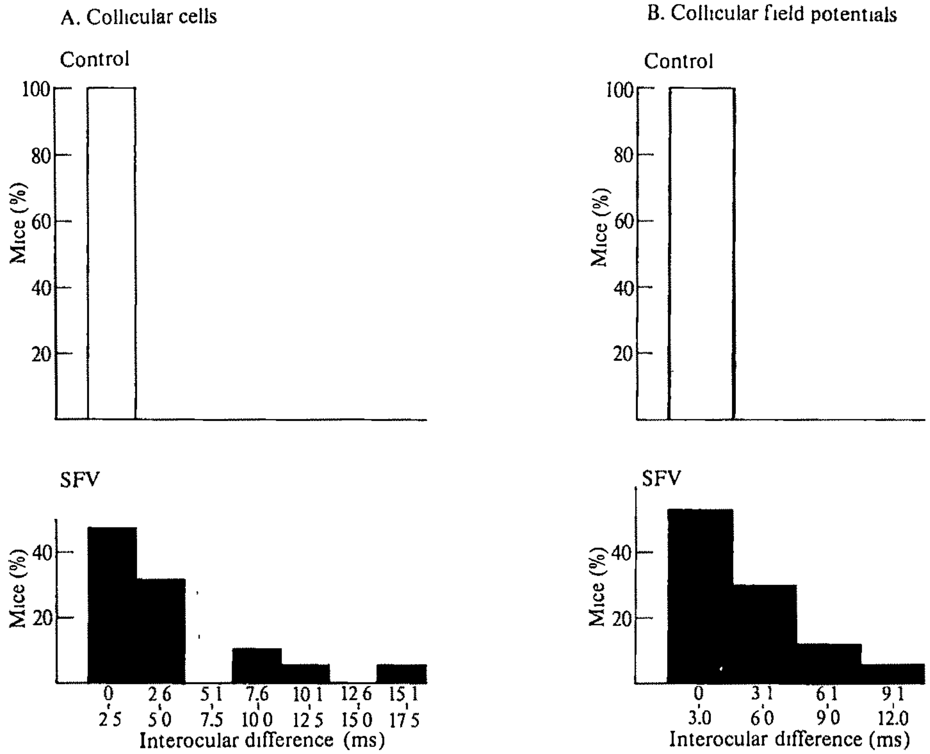

FIG 3. Histograms showing the percentage of mice with the given interocular difference in visual latency shown on the abscissa. For collicular cells the interocular difference was calculated as the difference in mean visual latency of cells from the left eye and of cells from the right eye in each mouse. For collicular field potentials the interocular difference was calculated as the difference in mean visual latency of penetrations from the left eye and of penetrations from the right eye in each mouse.

Interocular difference in visual latency. It was noted during the experiments that the visual latencies of collicular cells or field potentials evoked from the left and right superior colliculi in control mice did not differ greatly, whereas interocular differences seemed greater in SFV infected mice. Thus, we have studied the difference in visual latencies of collicular cells and field potentials recorded in the left and right colliculi responding to the right and left eye, respectively, to see whether the difference was significantly larger in the infected animals than in the controls. The results of this analysis are shown in fig. 3.

Fig. 3 shows the distribution of the interocular differences in mean visual latencies obtained for different mice. For both the single collicular cells and the field potentials, the maximum interocular difference in visual latency for the control mice is as small as 3 ms, whereas the histograms are again skewed to the right for the SFV infected mice. An interocular difference as great as 16 ms was found. Eight control mice and 15 SFV infected mice contributed to the collicular cell data, 10 control mice and 17 SFV infected mice, to the collicular field potential data.

Visual latency-intensity function. It is well known that the greater the light intensity, the shorter is the response latency of visual neurons. Is the latency-intensity function affected in our animal model of demyelination?

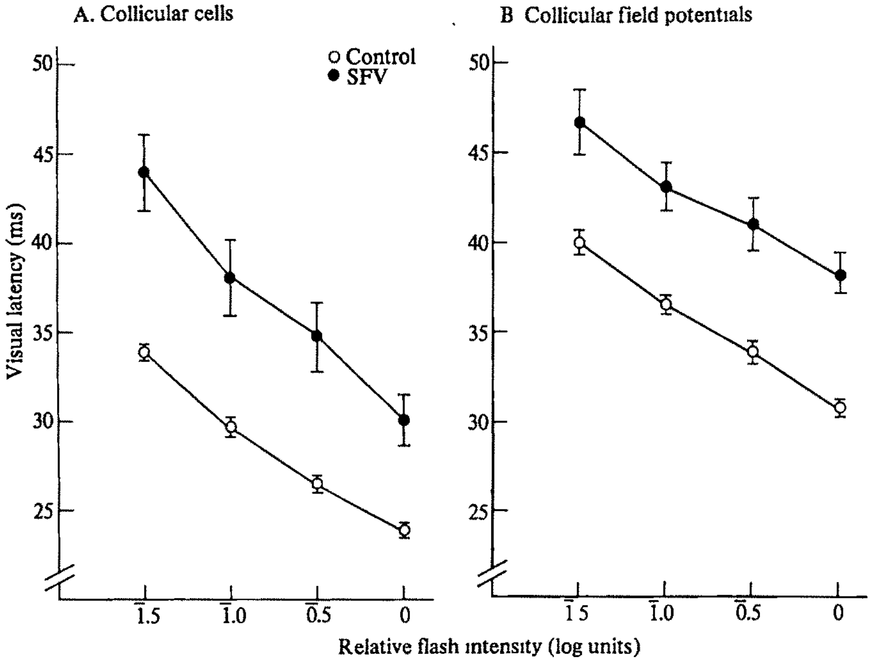

FIG. 4. Visual latency as a function of stimulus light intensity for collicular cells (A) and collicular field potentials (B). Each point in A is the mean and standard error of 25 cells recorded from 9 control mice and 75 cells recorded from 18 SFV infected mice, and in B of 22 penetrations recorded from 12 control mice and 23 penetrations recorded from 12 SFV infected mice. Data from left and right hemispheres were combined.

Fig. 4 shows the visual latency of the superior collicular cells (A) and that of the field potentials (B) as a function of relative intensity of the light stimulus. The cells or the field potentials obtained from the control mice show a good rectilinear function with a slope of approximately -0.7. The functions obtained from the superior colliculi of the infected mice are shifted upwards towards longer latency, but with the same slope.

Response magnitude and intensity function—sensitivity to light. Fig. 5A shows field potentials recorded from the superior colliculus of a control mouse (age 51 days) and a SFV infected mouse (age 52 days) at different light intensities. The responses from the SFV infected mouse are smaller and broader than those from the control mouse at a given intensity.

Fig. 5B combines data from all control mice (12 mice, 22 penetrations) and all infected mice (12 mice, 23 penetrations). It shows the amplitude of the field

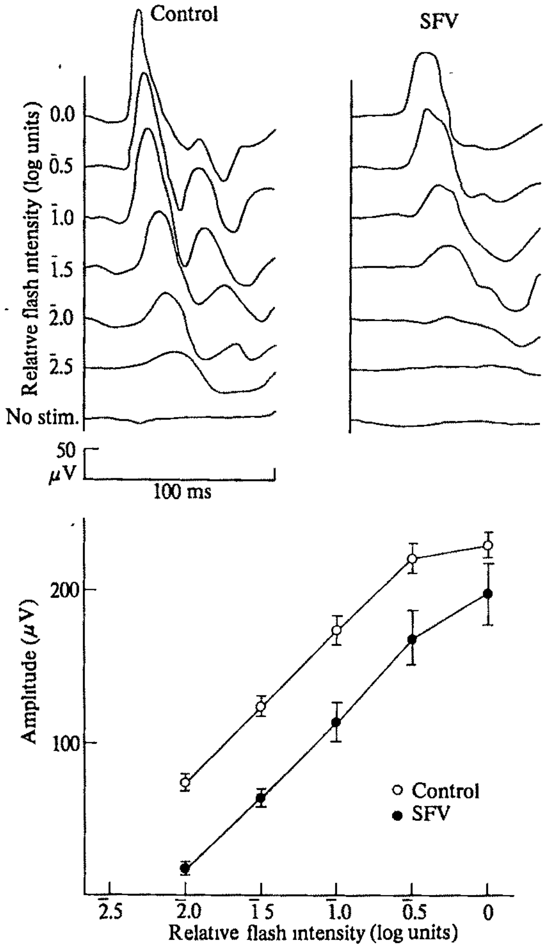

FIG 5. Amplitude-intensity function. In the upper two panels are field potentials recorded at different flash intensities from the superior colliculus of a control mouse and a mouse infected with SFV. The lower panel shows the mean amplitude and standard error of field potentials as a function of stimulus light intensity. Data from left and right eyes were combined.

potentials as a function of the stimulus intensity. By extrapolation it can be seen that the threshold intensity for the infected animals is raised by approximately 0.5 log units.

Temporal resolution of visual cells in the superior colliculus. Fig. 6A shows poststimulus histogram responses obtained from collicular cells recorded from a control mouse (age 52 days) and from a mouse infected with SFV (age 53 days). The stimulus was an optimal spot at the receptive field centre flickering at different frequencies. Both the cell from the control mouse and that from the infected mouse had receptive fields in the inferior nasal quadrant of the visual field. The cell from the control mouse showed clear responses to individual flashes up to 30 Hz, whereas the cell from the infected mouse showed no response at 25 Hz.

Fig. 6B shows field potentials recorded from a control mouse (age 50 days) and also from a SFV infected mouse (age 51 days), using a diffuse flash flickering at different rates. Again, the field potentials from the control mouse showed clear

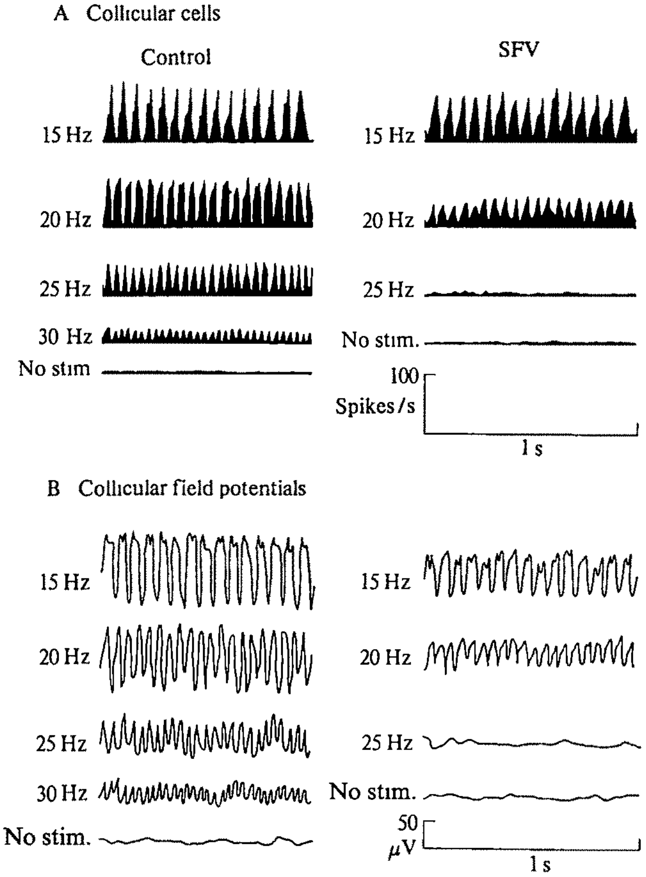

FIG. 6. Response to rapid light stimulation (flicker). A shows post-stimulus histogram responses of a collicular cell from a control mouse and a collicular cell from an SFV infected mouse responding to a spot of optimal size and intensity flashing at the receptive field centre at different flashing rates. Each histogram was constructed over 64 sweeps. B shows field potentials (averaged over 64 sweeps) from the superior colliculus of a control mouse and from an SFV infected mouse evoked by a diffuse flash of optimal intensity covering 100 deg of the visual field, and flashed at different rates.

wavelets at 30 Hz, whereas those from the infected mouse showed early fusion at 25 Hz.

Fig. 7A and B summarize the data obtained from experiments on flicker fusion frequency as a function of flash intensity as determined from poststimulus histogram responses of single collicular cells (21 cells from 9 control and 47 cells from 18 infected mice) and also from field potentials (18 penetrations in 12 control mice and 20 penetrations in 12 SFV infected mice). According to the Ferry-Porter Law, temporal resolution, as determined by the critical flicker fusion frequency, that is, the flicker rate which the visual system just ceases to follow, depends upon the flash intensity: the higher the intensity of the flash, the higher the flicker fusion frequency. This function is also affected in the SFV infected mice.

For both single cells and field potentials the ability to follow high rates of flicker, that is, temporal resolution, is significantly depressed in the infected mice.

Studies in Patients

To compare the results of collicular neurons in SFV infected mice with the behaviour of the VEP in patients with demyelinating disease, the VEP was recorded

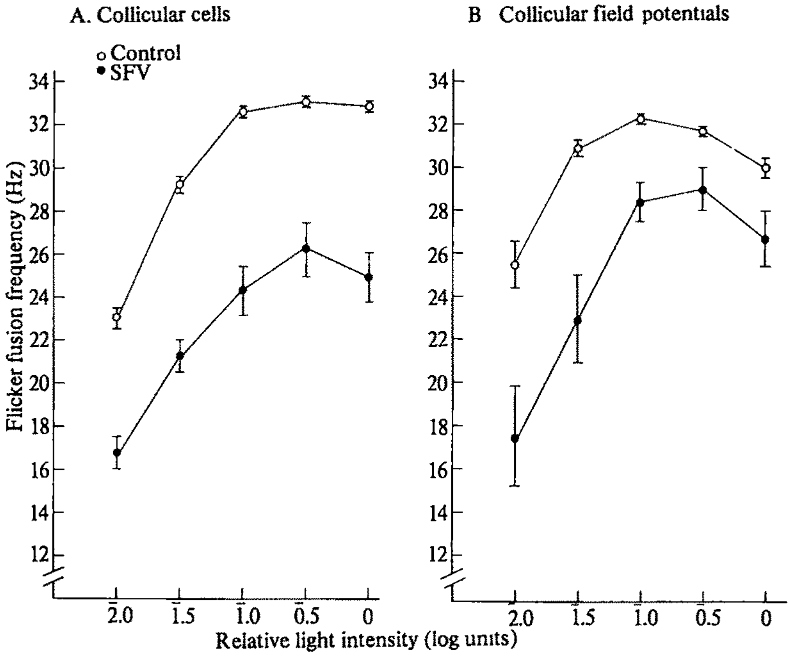

FIG. 7. Flicker fusion frequency of collicular cells (A) and collicular field potentials (B) as a function of a stimulus light intensity. The flicker fusion frequency is the highest frequency at which the cell just fails to respond to the stimulus. Data from left and right eyes were combined.

in patients, using the same flash stimuli as those used in the mouse. These patients were referred to our electrodiagnostic clinic with suspected demyelinating disease for VEP assessment during 1981. Twenty-four patients were classified as having unaffected optic nerves on the basis of pattern evoked VEPs with normal amplitudes and latencies. Forty-seven patients showed delayed pattern evoked VEPs in one or both eyes. These patients were finally diagnosed as having multiple sclerosis (MS), by the referring consultant neurologist, according to clinical criteria (*see* McDonald, 1975).

Fig. 8 (left) shows flash evoked VEPs of 3 patients, L.P., B.T. and M.W. The responses were evoked from each eye with a flash (intensity, 5×10^5 cd/m^2) at 4 Hz. The responses of patient L.P. were normal in both right and left eyes (right eye: amplitude 23.5 μV, peak latency 115 ms; left eye: amplitude 20.4 μV, peak latency 117 ms). In patient B.T., the VEP from the right eye was normal, whereas that from the left eye had a broader waveform and delayed peak, compared with the right (right eye: amplitude 10.9 μV, peak latency 115 ms; left eye: amplitude 9.6 μV, peak latency 125 ms). The last patient, M.W., showed subnormal and delayed flash VEPs in both eyes (right eye: amplitude 9.0 μV, peak latency 150 ms; left eye: amplitude 9.0 μV, peak latency 155 ms).

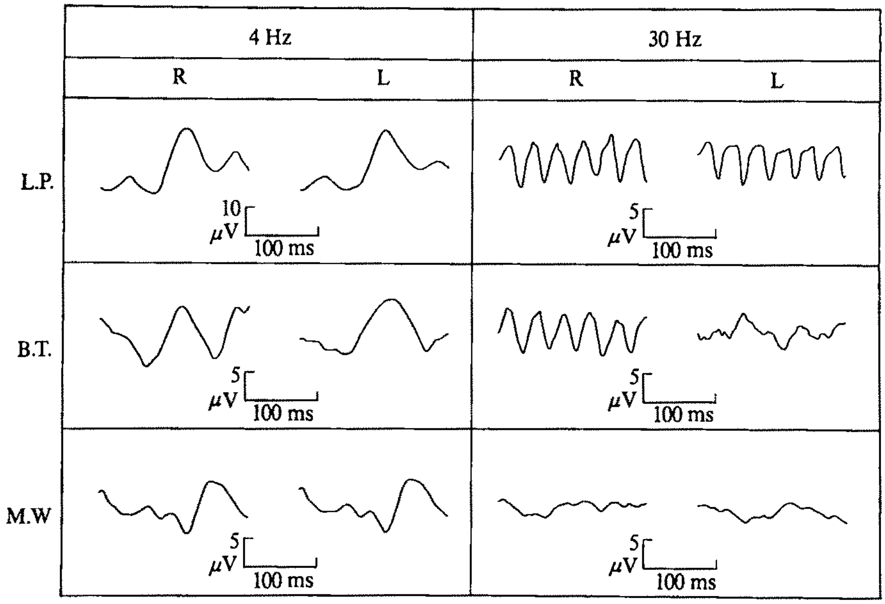

FIG. 8. Flash evoked VEPs of 3 patients, LP., B.T and M.W. On the left are VEPs evoked by 4 Hz flash in the right (R) and left (L) eye. On the right are VEPs evoked by 30 Hz flicker in each eye. Each record is the average of 100 sweeps. *See text* for details of the patients.

Fig. 8 (right) illustrates VEPs of the same patients responding to a flickering light at 30 Hz. In patient L.P., clear flicker VEP wavelets of high amplitude (right eye: 7.6 μV; left eye: 6.4 μV) were obtained, although the wavelets for the left eye were slightly broader. The flicker VEPs from the right eye of patient B.T. were still following 30 Hz flicker (7.0 μV), whereas in the records from the left eye, no clear flicker response could be seen. The responses from patient M.W., were already fused for both eyes.

Patient L.P. was a 23-year-old nurse. Internuclear ophthalmoplegia was noted in April 1979, but this recovered completely in June 1980, although she still has episodes of tingling in the right arm. X-rays of skull, cervical spine and chest, and serum B_{12}, were normal; the CSF and blood VDRL and TPHA tests and an autoantibody screen were negative. A slightly raised lymphocyte count was found on one occasion. In October 1980, she had an episode of loss of consciousness of unknown cause. The patient was referred for VEPs because of the possibility of a demyelinating condition. The pattern VEPs recorded in May 1981 were normal bilaterally. Visual acuities were 6/4 in each eye; normal fundi and normal visual fields. No firm diagnosis had been reached for this patient.

Patient B.T., a 25-year-old housewife, had a story of blurred vision in the left eye, restricted movement on upward gaze, an afferent pupillary defect and upper temporal sectorial visual field defect in the left eye. Optic discs, acuities and all other examinations were normal, except that the CSF IgG concentration was slightly raised. Pattern VEPs, as well as flash VEPs, were recorded in September 1981 at the time when her vision had recovered. The VEP results were consistent with significant left optic neuritis. She also complained of bladder difficulties and slight intermittent numbness in the right leg. She was subsequently diagnosed as MS since she had (1) remitting and relapsing signs; (2) multiple lesions; (3) CSF results suggestive of demyelinating disease and (4) delayed VEP and pupillary light reflex.

Patient M.W., a 49-year-old housewife, was suspected of having MS because of transient loss of vision in the left eye in 1977. During 1980–1981 spastic ataxia of her limbs developed. Her condition progressively deteriorated, but CSF examination revealed no definite abnormality. Visual acuities were 6/9 in the right and 6/6 in the left eye. VEPs were recorded in June 1981 and both pattern and flash evoked responses were subnormal and delayed bilaterally. In October 1981, she had a further attack of blurred vision, this time in the right eye but her vision improved over six weeks. Her ataxia progressively worsened and she now has walking difficulties. On the basis of multiple lesions and remitting and relapsing signs, together with the VEP results, she was diagnosed as MS.

The mean peak latency (the equivalent measure to that of peak latency of the collicular field potential—*see* fig. 1B) of the flash VEP to the 4 Hz stimulation in the 24 patients with normal pattern VEPs was 113.6 ms ± 0.80 SE ($n = 48$), whereas that in the 47 patients with the diagnosis of MS was 132.1 ms ± 1.9 SE ($n = 76$), when the data for all affected eyes were combined.

The mean amplitude of the flicker VEP in these 47 patients (all affected eyes combined) was 2.20 μV ± 0.19 SE ($n = 76$), whereas the mean amplitude of the flicker VEP in those patients with normal pattern VEPs (all eyes combined) was 4.39 μV ± 0.32 SE ($n = 48$). The flicker VEP is therefore significantly lower.

Thus, as in SFV infected mice, the peak latency of the flash VEP is significantly longer ($P < 0.001$) and the flicker VEP is significantly lower ($P < 0.001$) in patients with the diagnosis of multiple sclerosis compared with the unaffected group. As the severely affected eyes such as those illustrated in fig. 8 demonstrate, the VEPs of some patients showed a total inability to follow the 30 Hz flicker.

DISCUSSION

We have observed a significant increase in visual latency at the level of the single collicular cell and in collicular field potentials in mice infected with Semliki Forest virus (SFV). This observation provides physiological evidence for the demyelination in the optic nerve observed histologically in these animals (Illavia *et al.*, 1982; Fleming *et al.*, 1982). These findings, furthermore, confirm the usefulness of the measurement of delay in the peak time of the visual evoked potential (VEP) in diagnosing demyelinating disease. As for the pattern VEP recorded from patients with multiple sclerosis, Ikeda *et al.* (1978) found that interocular differences in peak times were significantly greater in these patients than in control subjects. It is interesting that interocular differences in visual latency were also present in our animal model of patchy demyelination in the optic nerve which one might expect to be generalized and bilateral in nature.

A further interesting feature of our animal model is the loss of temporal resolution of collicular cells and field potentials (fig. 6), since this is also one of the main physiological findings in patients with multiple sclerosis (Celesia and Daly, 1977; Cohen *et al.*, 1980). Indeed, we demonstrated that such patients also respond poorly to a high frequency flicker stimulus similar to that used in the mice experiments.

Moreover, these physiological results, indicating a significant loss in temporal resolving power of the visual system in demyelinating disease, correlate with a loss in critical flicker fusion frequency determined psychophysically by Parsons and Miller (1957). This may be related to the inability to transmit rapid trains of impulses in demyelinated nerve fibres which has been demonstrated in many other animal models of demyelination, such as the sciatic nerve of Trembler mice with chronic demyelination (Low and McLeod, 1977), diphtheria induced demyelination in rat ventral root (Rasminsky and Sears, 1972) and in cat spinal cord (McDonald and Sears, 1970), as well as in the peripheral nerves of guinea pigs during experimental allergic neuritis (Davis, 1972). In fact, Rasminsky and Sears (1972) demonstrated, in single demyelinated fibres of rat ventral root, that continued repetitive stimulation progressively increased internodal conduction time until conduction was finally blocked.

There have been several previous descriptions of optic neuritis in an animal model of demyelinating disease. Pathological changes have been observed in the optic nerve of strain 13 guinea pigs with chronic experimental allergic encephalomyelitis (Raine *et al.*, 1980) and with chronic experimental allergic optic neuritis (Rao, 1981). No electrophysiological investigations were attempted in these studies.

Hayreh *et al.* (1981), who evaluated optic neuritis in monkeys with experimental allergic encephalomyelitis by ophthalmoscopic, fluorescein fundus angiographic, pupillary light reflex, visual evoked potential, neurological, cerebrospinal fluid and haematological examinations, found that the flash visual evoked potential showed an overall prolongation of peak time with the development of optic nerve demyelination. These authors also demonstrated that the VEP results correlated with the degree of demyelination found histologically in the optic nerves of these animals.

The visual latency-intensity function of the VEP has not been studied extensively studied in patients with multiple sclerosis, except that Cant *et al.* (1978) found that in some patients, the VEP latency was prolonged at all intensities. The visual latency-intensity functions derived from the present experiments in mice (fig. 4) also show this feature.

Fig. 5, furthermore, shows that the visual threshold in SFV infected animals, as determined by the responses of collicular cells and field potentials, was raised by about 0.5 log units. Visual thresholds determined psychophysically are sometimes elevated in multiple sclerosis. Raised thresholds have been reported by Burde and Gallin (1975) in the affected eyes of patients with previous retrobulbar neuritis. Patterson *et al.* (1980) measured psychophysical visual thresholds at four different background luminance levels in patients with multiple sclerosis and found that the patients' threshold was significantly raised only at the highest background luminance level.

Although the behaviour of the collicular cells in mice infected with SFV is indeed consistent with that expected from demyelination of the optic nerve fibres, whether or not they could be entirely attributed to optic nerve demyelination needs to be questioned. Despite the presence of high virus titres, Illavia *et al.* (1982) found no obvious pathological changes in the retinas of SFV infected mice. Similarly, in monkeys with experimental allergic encephalomyelitis, no evidence of inflammatory infiltration in the retina or around the retinal vessels was obtained by Hayreh *et al.* (1981). However, the absence of pathological changes does not necessarily mean that there is no physiological change in the retina. Obviously only systematic studies of the electroretinogram together with collicular field potential studies at the different stages of SFV infection in our experimental model can answer this problem. Indeed our preliminary experiments suggest that there may be dynamic changes in the retinal physiology during the course of SFV infection (E. M. Tansey, E. Oswaldo-Cruz and H. Ikeda, unpublished results). We therefore cannot exclude the possibility of a direct effect on the retina influencing the results obtained at the superior colliculus in the present experiment.

To conclude, it appears that virus-induced demyelination in the mouse is accompanied by neurophysiologically demonstrable visual deficits very similar to those found in patients with multiple sclerosis. This may, therefore, provide a useful animal model for research into multiple sclerosis. The advantages of this model are that genetic and environmental factors can be readily controlled, while the low cost and fast reproductive rate of the animals makes experimental design relatively simple. We hope, in future experiments, to describe in more detail the time course of the disease process and to determine the early physiological changes that occur immediately after viral infection.

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SURFACE RECORDING OF THE SPINAL VENTRAL ROOT DISCHARGE IN MAN

AN EXPERIMENTAL STUDY

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SUMMARY

The response evoked by stimulation of the tibial nerve was recorded by surface electrodes over the lumbosacral spine at multiple levels with both monopolar and bipolar recordings.

When the stimulus strength was adjusted to elicit a maximal H reflex, bipolar recordings showed a negative-positive deflection (W_1), increasing in latency in the rostral direction and classically attributed to the propagated action potentials in the dorsal roots, followed by a previously unreported positive-negative deflection (W_3) showing the opposite sequence, namely, with latency decreasing in the rostral direction. A similar pattern was found in monopolar recordings in which, however, the peak corresponding in time to W_3 was partially obscured by a fixed latency component (W_2), particularly prominent over the upper lumbar vertebrae.

When an intensity corresponding to the maximal M wave was employed, W_2 showed a remarkable increase in amplitude, while both W_3 and the H reflex disappeared. Several experimental techniques, either suppressing or enhancing the H response, confirmed the strict parallelism existing between this reflex and the W_3 component.

These findings suggest that W_3 represents the reflexly evoked ventral root discharge. This was confirmed by concurrent intrathecal and surface recordings of the lumbosacral spinal evoked activity. W_2 is probably generated by the postsynaptic activation of spinal neurons located in segments receiving the tibial nerve afferents, the motoneuronal contribution to this fixed latency component being slight or absent.

INTRODUCTION

Following the pioneer study by Magladery *et al.* (1951), who obtained intrathecal recordings of action potentials from both dorsal and ventral spinal roots upon stimulation of the tibial nerve in humans, there has been an increasing interest in the surface recording of the lumbosacral response (LSR) as a suitable method of investigating the input-output relationships in the spinal cord. To this purpose Delbeke *et al.* (1978), taking advantage of the anatomical features of the lumbosacral region in which substantial lengths of dorsal and ventral roots are available, tried to correlate the lumbosacral response with the H reflex. In particular, they claimed that the first negative deflection of the LSR is caused by action potentials conducted in sensory fibres of the dorsal roots, while the second negative peak is a reflexly elicited volley in the ventral root fibres. It was rightly pointed out (Phillips and Daube, 1980), however, that if the two negative peaks of the LSR were the afferent and the efferent limbs of the H reflex arc, the first should show a progressive increase in latency in recordings from more rostral sites, while the latency of the second should progressively decrease, as demonstrated by intrathecal recordings (Magladery *et al.*, 1951). According to the data so far available, this holds true only for the first peak: in fact, the latency of the second is remarkably constant throughout the lumbosacral spine (Dimitrijevic *et al.*, 1978; El Negamy and Sedgwick, 1978; Phillips and Daube, 1980). On these grounds it might be contended that surface recordings can detect dorsal root activity but are unsuitable for recording the ventral root discharge, although no satisfactory explanation for this apparent discrepancy has been offered.

The present investigation shows that, providing a stimulation of suitable intensity is used, a component of the LSR showing a significant *decrease* in latency from caudal to rostral sites can be detected in surface recordings, and that a satisfactory parallelism between its amplitude and that of the H reflex can be found under appropriate experimental conditions. In brief, it will be shown that reproducible surface recordings of the ventral spinal root discharge can be obtained in humans.

MATERIAL AND METHODS

Experiments were conducted in a quiet room on 8 healthy volunteers (informed consent) of both sexes, aged 26 to 34 years; some were examined on several occasions. During the experiment the subjects lay prone on a couch with the head rotated towards the stimulated side. The legs were gently warmed by an infrared lamp throughout the experiment to ensure a skin temperature of 36 to 38° C. The tibial nerve was stimulated in the popliteal fossa using surface electrodes positioned on the anteroposterior axis with the cathode (2 cm^2) placed in the popliteal fossa and the anode (20 cm^2) attached over the patella. Square wave pulses were delivered by Disa 14 E 01 Ministim stimulator (pulse duration 0.5 ms) at a rate of 0.5 Hz, except when the effects of increasing frequencies (from 0.5 to 5.0 Hz) or of post-tetanic potentiation (following a 20 s tetanus at 200 Hz) were studied. The stimulus intensity was adjusted to elicit either a maximal M response or a maximal H reflex, the whole range of intensities being used when the recruitment curve of the lumbosacral and the electromyographic (i.e., H and M) responses were concurrently investigated. In no case was it necessary to use intensities higher than 30 mA.

Surface recordings of lumbosacral activity were performed by means of fine bare subcutaneous needles, with an electrode impedance of 1000 to 2000 Ω. Monopolar recordings were obtained with the active (G_1) electrode placed over the spinous processes of S2, S1, L5, L4, L3, L2, L1, T12 and T11 and with the reference (G_2) electrode positioned over T6. Sequential bipolar recordings were obtained from electrode pairs (the interelectrode distance varying from 5 to 7 cm) placed over the spinous processes of S2, S1, L5, L4, L3, L2, L1, T12, T11, T10 and T9, the caudal lead of each electrode pair being connected to the input terminal 1 of the amplifier.

Intrathecal recordings were performed through the bare tips of long insulated steel needles (Disa 13 L 63) placed within the spinal theca across the interspaces L2-L3, L3-L4, L4-L5, a fine subcutaneous bare needle, positioned in close proximity of the intrathecal one at the same vertebral level, being used as the reference electrode

Simultaneous recordings of the electromyographic responses (i.e. H and M) were obtained by surface electrodes (Disa 13 K 60) placed 3 cm apart on the skin over the soleus muscle, the active lead being proximal.

The input from the lumbosacral recording electrodes was fed into differential amplifiers (Evoked Potential Amplifier Ote 2305) and simultaneously recorded on magnetic tape (Philips Analog 7). The frequency response of the recording apparatus was 16 to 10 000 Hz (3 dB). Analysis times of 20 or 50 ms were used and usually 128 or 256 responses were summated by means of a Neuroaverager Ote 1239 and displayed on a X-Y Plotter (Philips PM 8125). Number, shape and polarity of the recorded potentials were analysed visually. Peak latencies were measured on the plot or with a cursor on the computer oscilloscope. The electromyographic responses were amplified, averaged and displayed by a Disa System 1500.

Vibration of the calf muscle on the stimulated side was undertaken by means of a cylindrical vibrator (Heiva, Model TMT 18) (vibration frequency 100 Hz, amplitude 2 mm) applied with a constant pressure over the Achilles tendon.

The results were evaluated statistically by means of one way analysis of variance for repeated measures (Winer, 1971).

RESULTS

The potentials evoked by stimulation of the tibial nerve were recorded from the lumbosacral spine at multiple levels with both monopolar and bipolar recordings. Well defined, reproducible responses were obtained in all subjects. In each case, the stimulus strength was adjusted to elicit either a maximal motor (M) response or a maximal H reflex.

The Lumbosacral Response at a Stimulus Strength Corresponding to the Maximum M Wave

With a stimulus intensity that elicited a maximal M response, monopolar recordings (fig. 1A) showed a waveform essentially similar to that of previous descriptions, this being characterized by two negative peaks (W_1 and W_2), the time interval between which progressively decreased rostrally (from 3.8 ± 0.5 ms at S2 to 1.5 ± 0.5 ms at L1; $F = 9.228$, $P < 0.01$). To this account, it should be noted that: (1) the latency of W_1 increased significantly from 9.9 ± 0.5 ms at S2 to 12.1 ± 0.7 ms at L1 ($F = 9.356$, $P < 0.01$), while the latency of W_2 remained unchanged (13.7 ± 0.7 ms at S2 *vs* 13.6 ± 0.7 ms at L1; $F = 1.012$, n.s.); (2) the amplitude of W_1 decreased rostrally, the opposite being true for W_2, thus confirming previous investigations on the spatial distribution of the LSR in monopolar recordings (El Negamy and Sedgwick, 1978). Concurrent bipolar recordings (fig. 1B) were also basically characterized by a negative deflection, progressively increasing in latency from lower to upper recording sites, followed by a fixed latency component which was clearly visible only from L3 to L1 or T12 and showed a clear-cut phase reversal (apparently also observed by Cracco *et al.*, 1975; Jones and Small, 1978; and Phillips and Daube, 1980) at the L1 (or T12) level. In brief, both monopolar and bipolar recordings were characterized by a travelling wave (W_1) followed by a fixed latency component (W_2). At the T12 (or T11) level both monopolar and bipolar recordings (fig. 1A, B) showed a smooth, predominantly negative wave, coincident in time with

W_2, ending with a long-lasting positive deflection. According to Delbeke *et al.* (1978) and to Dimitrijevic *et al.* (1978) such an event can be identified with the S potential described by Magladery *et al.* (1951). In some cases a small negative deflection was distinguishable at the beginning or on the ascending limb of the S wave (fig. 1A, B), its latency being a little greater than that of W_1 at the L1 level. According to Magladery *et al.* (1951), such a deflection is likely to reflect the intraspinal activity of the same neurons that are responsible for W_1.

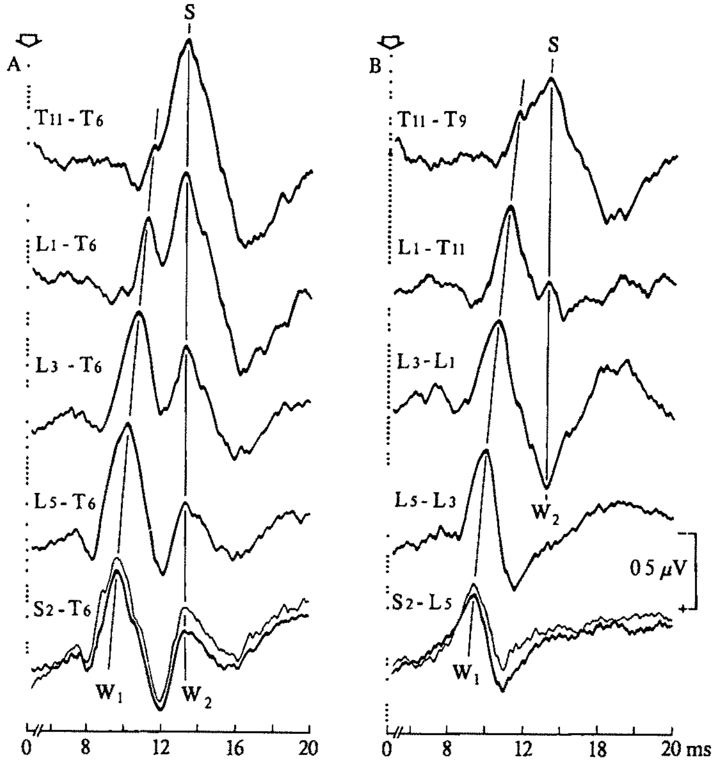

FIG 1. Monopolar (A) and bipolar (B) recordings of the potentials evoked by stimulation of the tibial nerve at the intensity eliciting a maximal M wave It should be noted that (1) both monopolar and bipolar recordings are characterized by a negative deflection (W_1), progressively increasing in latency from lower to upper recording sites, followed by a fixed latency component (W_2); (2) in bipolar recordings W_2 is clearly visible only from L3 (third trace) to L1 (second trace), showing a clear-cut phase reversal at the L1 level, (3) at the T11 level both monopolar and bipolar recordings consist of a smooth, predominantly negative wave (S), corresponding in time with W_2, ending with a long-lasting positive deflection. All the traces are the average of 128 responses In this and in fig. 3 two separate averages are superimposed in the lowest traces to show the reproducibility of the responses.

Double pulse experiments showed that at an interval of 8 ms there was a full recovery of W_1, while at the same interval the amplitude of W_2 did not exceed 50 per cent of the control response (fig. 2). Also the recovery of the S wave was only partial after 8 ms, whereas the early negative deflection, when visible, had fully recovered, thus suggesting that the S wave is mainly, but not exclusively, postsynaptic in origin.

The Lumbosacral Response at a Stimulus Strength Corresponding to the Maximum H Reflex

As is well known, at stimulus intensities yielding a maximal M wave the development of the ventral root discharge is prevented by the collision between the antidromic and reflex volleys in the most proximal part of the motor axon, which causes the extinction of the H reflex (Diamantopoulos and Gassel, 1965). This concept, as well as other lines of evidence (*see* Discussion), make it unlikely that W_2 reflects orthodromic ventral root activity. On the other hand, when the stimulus intensity is adjusted to elicit a maximal H reflex and the M response is small or absent, the collision between antidromic and reflex impulses becomes practically negligible. It follows that under such conditions the ventral root discharge should be detectable, possibly even by surface electrodes. At an intensity corresponding to the maximum H reflex the monopolar recordings in fact showed a waveform slightly different from that illustrated in fig. 1A. In particular, it was found (fig. 3A) that, while the features of the first negative peak (W_1) appeared substantially unchanged (including the latency, which increased from 9.8 ± 0.6 ms at S2 to 12.2 ± 0.8 ms at L1; $F = 14.237$, $P < 0.01$), apart from the amplitude obviously being proportional to the stimulus strength (compare fig. 1A with fig. 3A), the second negative deflection resolved into two peaks (W_2 and W_3) most clearly visible in the caudal recordings. It should be pointed out that, while the latency of W_2 remained unchanged (13.7 ± 0.7 ms at S2 *vs* 13.6 ± 0.7 ms at L1; $F = 1.036$, n.s.), W_3 appeared progressively earlier from caudal to rostral sites (from 15.5 ± 0.8 ms at S2 to 14.0 ± 0.7 at L3; $F = 8.193$, $P < 0.01$). Over the upper lumbar vertebrae, W_3 seemed to be obscured by the progressive increase in amplitude of W_2, so that only a single negative peak could be recorded (fig. 3A, second and third traces). At the T12 (or T11) level, monopolar (as well as bipolar) recordings (fig. 3A, B) were characterized by a smooth negative-positive wave apparently corresponding to the S potential obtained at stimulus intensities yielding a maximal M wave. Also the concurrent bipolar recordings (fig. 3B) showed a waveform quite different from that illustrated in fig. 1B, particularly in

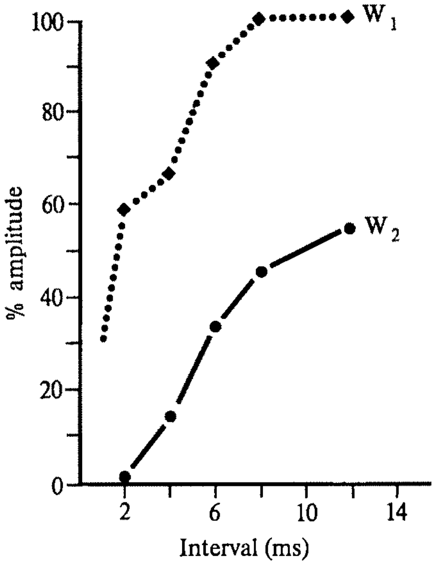

FIG. 2. Relationship between response amplitude and stimulus interval during a double pulse experiment showing that there was a full recovery of W_1 at an interval of 8 ms, while the amplitude of W_2 was still less than 50 per cent of its control value. The amplitudes of W_1 and W_3 are plotted as a percentage of the corresponding test response

the caudal recordings, where the response was characterized by a negative-positive deflection followed by a positive-negative one. It should be noted that the first negative peak increased in latency in the rostral direction (from 9.4 ± 0.6 ms at S2 to 11.6 ± 0.7 ms at L1; $F = 10.149$, $P = 0.01$), while the second peak showed just the opposite trend (from 15.9 ± 0.8 ms at S2 to 14.1 ± 0.8 ms at L3; $F = 8.173$, $P < 0.01$), thus behaving as W_1 and W_3, respectively. The minor chronological differences between bipolar and monopolar recordings can be ascribed to the recording technique. It was frequently observed that at L3 (or L2) level the waveform was altered by a downward displacement of the baseline, probably related to spreading of the S wave, the latter being seen as initially positive (in fig. 3B, compare the first with the third trace) due to the electrode position with respect to the (presumed) generator site. In particular, such a positive deflection, apparently reflecting the potential gradient of a fixed large amplitude lower thoracolumbar response, was superimposed upon two travelling waves (fig. 3B, third trace) and appeared coincident in time with second negative peak in monopolar recordings, that is, W_2. When bipolar recordings were obtained between L1 and T11, no displacement of the baseline occurred (fig. 3B, second trace), whereas a small negative deflection coincident with W_2 could be detected.

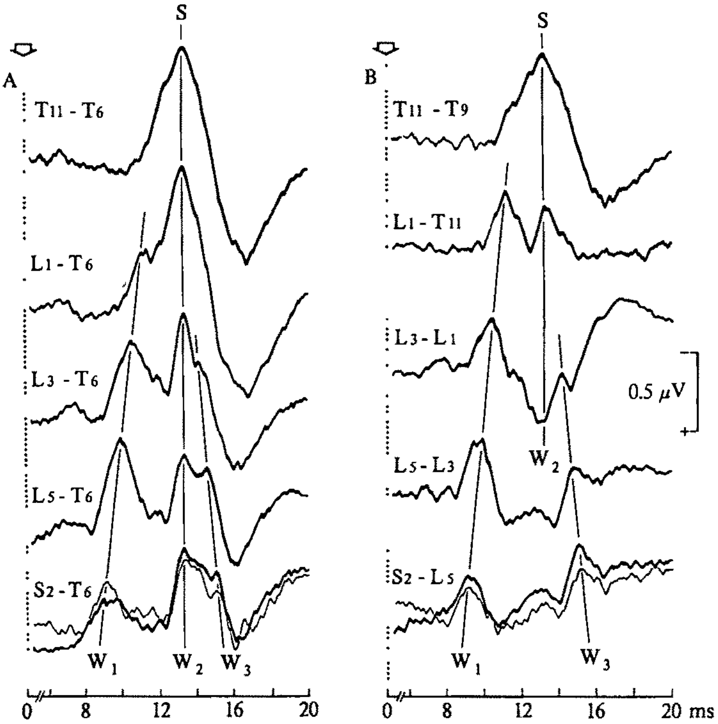

FIG. 3. Recordings from same subject illustrated in fig. 1 showing monopolar (A) and bipolar (B) recordings of the potentials evoked by stimulation of the tibial nerve at an intensity eliciting a maximal H reflex. It should be noted that (1) in the caudal monopolar recordings, W_1 is followed by a negative deflection that splits into two peaks (W_2 and W_3); (2) in the caudal bipolar recordings a negative-positive deflection (W_1) is followed by a positive-negative one (W_3), W_2 being distinguishable at L3 and L1 levels; (3) in both monopolar and bipolar recordings the latency of W_1 is progressively increased in the rostral direction, while W_3 shows the opposite trend; (4) the fixed latency component (W_2), which is better recognized in monopolar recordings, appears chronologically coincident with the negative peak of the S wave, as shown in fig. 1.

In summary, when the stimulus intensity was adjusted to elicit the maximal H reflex, both monopolar and bipolar recordings were characterized by two travelling waves (W_1 and W_3) separated by a fixed latency component (W_2), best shown by monopolar recordings but recognizable also in bipolar ones at least at the L3 level (fig. 3B, third trace), and corresponding in time with the negative peak of the S wave.

Control Experiments

Since the appearance of W_3 occurred only when the stimulus intensity was adjusted to elicit the H reflex, a probable functional relationship between these two events should be considered. To clarify this issue, the behaviour of W_3 was investigated under several experimental conditions known to affect the H reflex, the latter being concurrently monitored. In each case an intensity corresponding to the maximal H reflex was used.

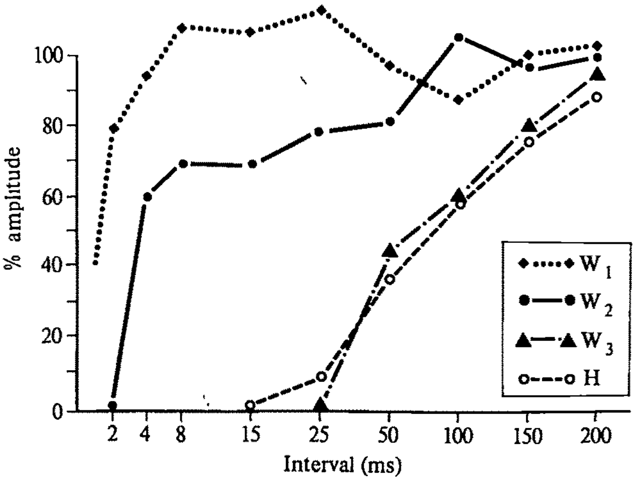

FIG. 4. Relationship between response amplitude and stimulus interval showing the recovery curves of W_1, W_2, W_3 and H reflex during an H-H conditioning experiment. It should be noted that both W_1 and W_2 recover much earlier than W_3 and the H reflex, the two latter events showing parallel changes in amplitude. The amplitude of each response is plotted as a percentage of the size of the corresponding test response.

(1) During the H-H conditioning experiments the W_3 component and H reflex showed parallel changes; moreover, it was observed that there was full recovery of W_2 at an interval of about 100 ms, whereas the amplitude of both W_3 and the H reflex did not exceed 50 per cent of the respective control responses (fig. 4).

(2) When the intensity of the stimulus was further increased, a progressive suppression of both W_3 and the H reflex was consistently observed until they completely disappeared (figs. 5A, 6) whereas, conversely, W_2 showed a further enhancement (fig. 6).

(3) A relatively slight increase in the stimulation frequency (from 0.5 to 5.0 Hz) produced a significant reduction in amplitude both of W_3 and the H reflex (fig. 5B).

(4) During calf muscle vibration, W_3 and the H reflex showed a parallel decrease in amplitude (fig. 7A), while the Jendrassik manoeuvre produced a clear-cut

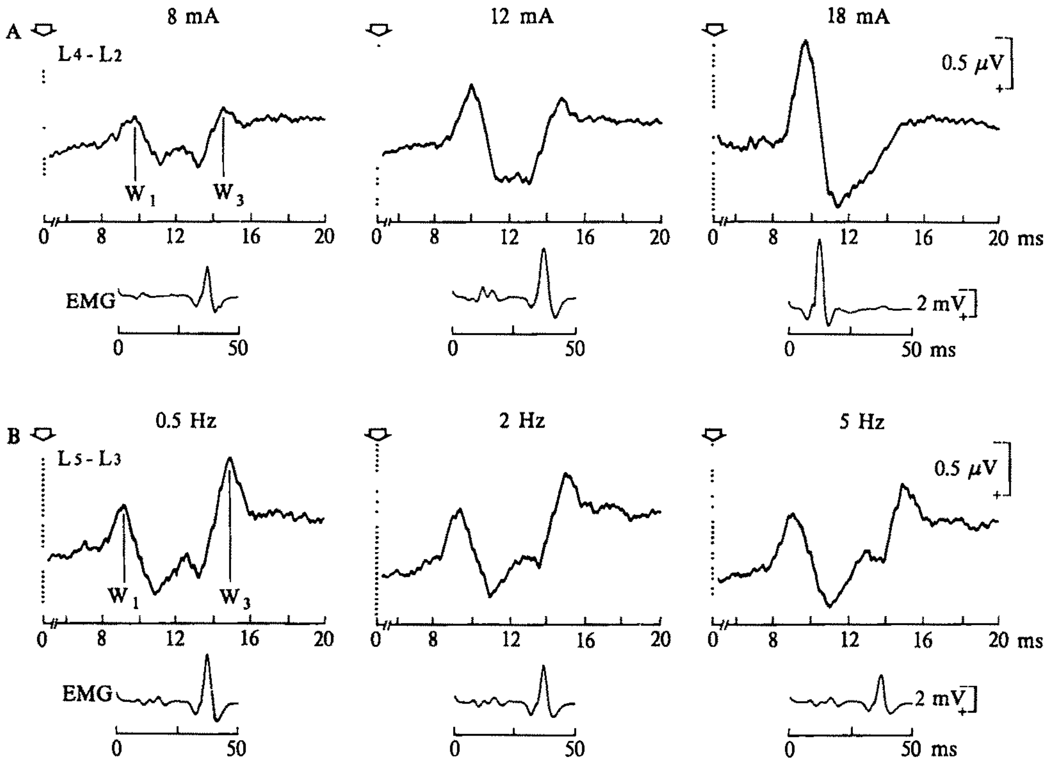

FIG 5. Recordings to show that W_3 and H reflex (EMG) display parallel changes in amplitude when the intensity (A) or the frequency (B) of the stimulus are increased.

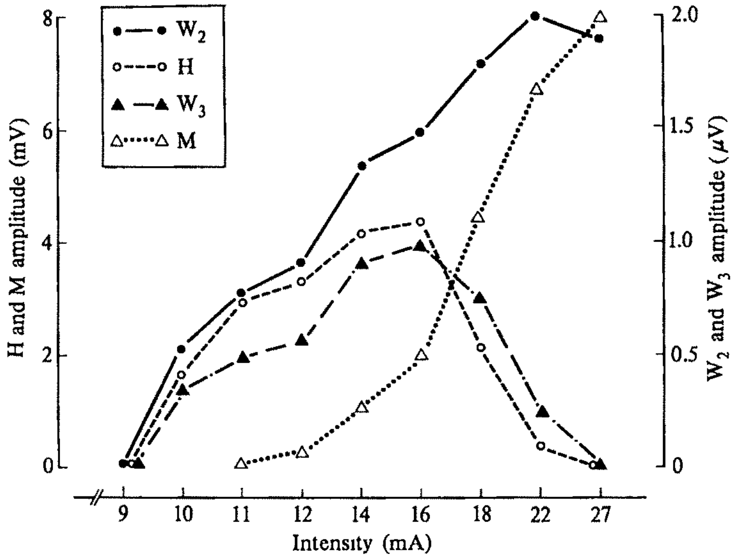

FIG. 6. H, M, W_2 and W_3 recruitment curves. It should be noted that (1) increasing stimulus strengths produces parallel changes in the amplitude of the H reflex and W_3; (2) when these responses begin to decrease, W_2 shows a further enhancement.

facilitation of both events (fig. 7B). Similarly, the post-tetanic potentiation of the H reflex was paralleled by a proportional enhancement of W_3.

In brief, all these findings confirm the existence of a functional relationship between W_3 and the H reflex and suggest the possibility that W_3 could represent the reflexly evoked ventral root discharge. Further support for this hypothesis was provided by concurrent intrathecal recordings obtained at L2, L3, L4 levels (fig. 8). As previously reported (Magladery *et al.*, 1951), their waveform was characterized by two negative deflections. According to these authors, the earlier potential (labelled as R) is produced by a synchronous volley of afferent impulses in the dorsal roots, while the second deflection (labelled as A) represents the reflex outflow through the anterior roots. We found that the R component occurred simultaneously with W_1 and the A component with W_3 (fig. 8), provided that the active leads were at the same vertebral level. Moreover, a consistent parallelism between changes in amplitude of the A and W_3 components under the different experimental conditions previously investigated was observed.

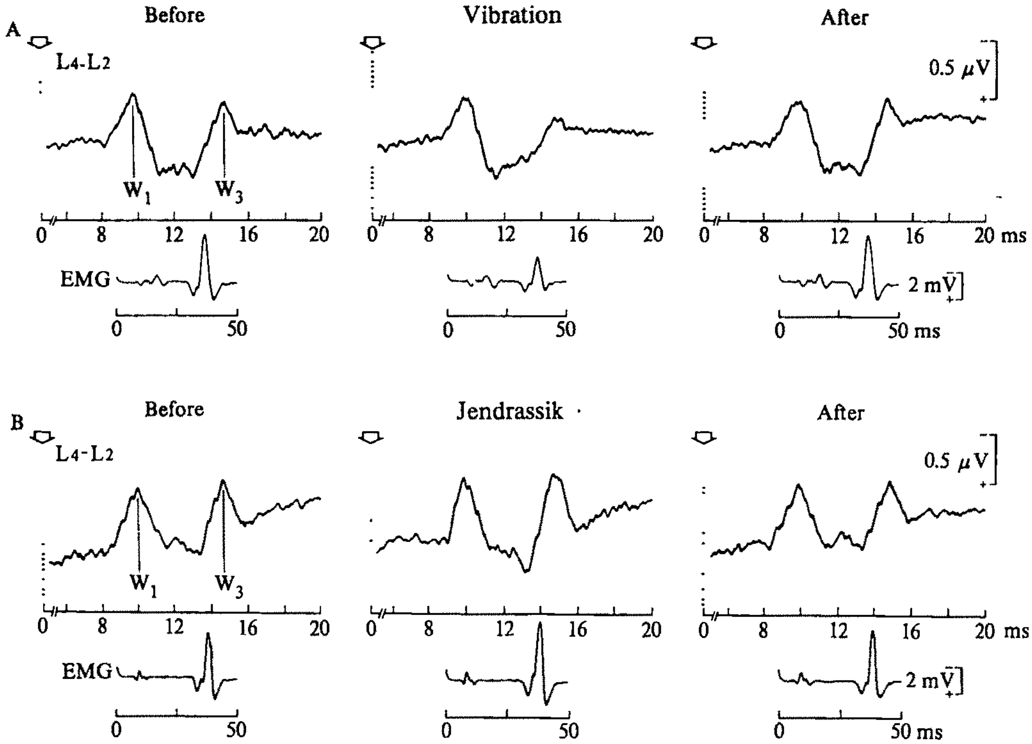

FIG. 7. A, recordings to show that during calf muscle vibration W_3 and the H reflex (EMG) show a parallel reduction in amplitude, whereas B, during the Jendrassik manoeuvre a clear-cut facilitation of both events is seen.

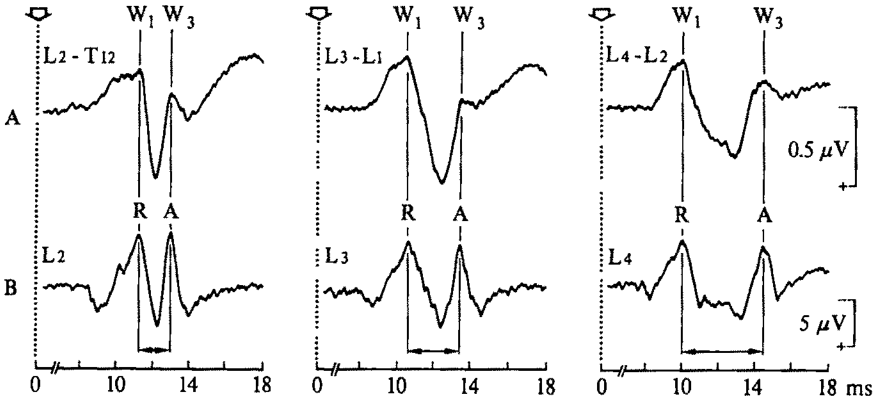

FIG. 8. A, concurrent surface and B, intrathecal recordings obtained at L2, L3 and L4 levels upon stimulation of the tibial nerve at an intensity eliciting a maximal H reflex. It should be noted that (1) at each level W_1 occurs simultaneously with the R component and W_3 with the A component, (2) both W_1-W_3 and R-A intervals become progressively reduced from lower to upper recording sites, the latencies of the W_1 and R components increase in the rostral direction, whereas those of the W_3 and A components show the opposite trend.

DISCUSSION

The general waveform of monopolar recordings from the lumbosacral spine was essentially similar to previous descriptions (Delbeke *et al.*, 1978; Dimitrijevic *et al.*, 1978; El Negamy and Sedgwick, 1978; Phillips and Daube, 1980), at least when a stimulus strength corresponding to the maximum M wave was used. There is little doubt that the progressive increase in latency of the first negative deflection (W_1) from lower to upper recording sites is the expression of an advancing wavefront of depolarization caused by propagated action potentials in the dorsal roots, as already suggested by Cracco *et al.* (1975), Delbeke *et al.* (1978), Dimitrijevic *et al.* (1978), El Negamy and Sedgwick (1978) and Phillips and Daube (1980). Some contribution from antidromic impulses in the alpha motor fibres should also be considered (Delbeke *et al.*, 1978), since stimulus intensities adequate to excite both afferent and efferent peripheral fibres were employed. Further support for these concepts was provided by double pulse experiments, which showed that W_1 has presynaptic properties, as demonstrated by El Negamy and Sedgwick (1978).

The hypothesis that W_2 is caused by a reflexly elicited volley in the ventral root fibres (Delbeke *et al.*, 1978) can be rejected. Should this be the case, the latency of W_2 in more rostral recordings would in fact progressively decrease. On the contrary, in monopolar recordings the latency of W_2 was remarkably constant throughout the lumbosacral region. An origin of W_2 from the spinal cord seems most likely, since the amplitude of this component increased progressively from lower to upper recording sites and its polarity showed a clear-cut phase reversal at the L1 (or T12) level. Indeed, these findings point to the existence of a fixed dipole located in the spinal cord, close to the thoracolumbar junction, thus confirming, at least in part, the conclusion reached by Phillips and Daube (1980). However, at variance with these authors who thought that W_2 was presynaptic, we were able to demonstrate that this component has postsynaptic properties, as already pointed out by El Negamy and Sedgwick (1978). The latter authors stated that the second negative component of the LSR is probably generated by the dorsal horn neurons. Thus they observed that at a stimulus strength sufficient to excite enough low threshold afferent fibres to produce a maximum H reflex, W_2 was very small, thus excluding the possibility that a relevant proportion of the motoneuronal pool could contribute to this potential. On the other hand, Delbeke *et al.* (1978) maintained that W_2 reflects the discharge of the anterior horn cells: indeed, they described a parallel change in the amplitudes of the W_2 component and the H reflex when stimulus intensity was varied. In our experience, however, at stimulus intensities yielding a maximal H reflex not only the amplitude but also the waveform of monopolar recordings differed considerably from those obtained by stimulus intensities eliciting a maximal M wave, W_1 being followed in the former instance by two peaks (W_2 and W_3), most clearly visible in the caudal recording sites (fig. 3A). It should be noted that the latency of W_3 decreased significantly from caudal to rostral sites, whereas the latency of W_2 remained unchanged. Concurrent bipolar recordings showed that the initial negative-positive deflection, progressively increasing in latency in the rostral direction, was followed by a previously unreported positive-negative deflection showing just the opposite trend, namely, a significant decrease in latency from lower to upper recording sites, thus paralleling the shifts in latency demonstrated respectively by W_1 and W_3 in monopolar recordings. Moreover, as in the latter case, a fixed latency component simultaneous with W_2 could be recognized, at least at upper lumbar levels. Finally, it seems of great relevance that the waveform of bipolar recordings was characterized by a negative-positive deflection followed by a positive-negative one. More specifically, since bipolar recordings were obtained by sequential electrode linkages with the caudal lead connected to the input terminal 1 of the amplifier, we think that the peculiar waveform produced by a stimulus intensity eliciting a maximal H reflex is the expression of a nerve volley in the cauda equina. This is at first propagated in a *rostral* direction, being then recorded as an initially negative diphasic potential since the caudal lead is reached by the ascending wavefront of depolarization earlier than the rostral one, and then in a *caudal* direction, the descending wavefront of depolarization reaching the caudal lead later than the rostral one, so that the nerve volley is recorded as an initially positive diphasic potential.

In other words, when the stimulus intensity was adjusted to elicit the maximal H reflex and the M response was small or absent, both monopolar and bipolar recordings were characterized by three waves, namely W_1, W_2, and W_3, the last of them being possibly related to the reflexly evoked ventral root discharge, since the latency decreased progressively in the rostral direction and its polarity, in bipolar recordings, was just reversed with respect to W_1, which is currently attributed to the dorsal root discharge. If this assumption is correct, it follows that any condition which reduces or enhances the H reflex should produce parallel changes in W_3.

Following these guidelines, a battery of relevant control experiments was employed. It was thus found that when either the intensity or the frequency of the stimulus was increased, a significant reduction in amplitude of both the W_3 component and the H reflex occurred. Similarly, calf muscle vibration decreased the amplitude of W_3 and of the H reflex, the opposite being observed during the Jendrassik manoeuvre and after a tetanizing train of stimuli. Finally, during the conditioning experiments the variations in amplitude of the W_3 component strictly paralleled those of the H reflex.

In brief, the constant similarity between the behaviour of these two events under different experimental conditions is consistent with the hypothesis that W_3 corresponds to the reflexly evoked ventral root discharge. Crucial proof was provided by concurrent intrathecal and surface recordings of the lumbosacral spinal evoked activity in which the A component showed a clear-cut coincidence with W_3, and a satisfactory parallelism between them under the experimental conditions mentioned above.

In summary, there is enough evidence to state that the spinal ventral root discharge can be detected by surface recordings, either bipolar or monopolar, provided that the stimulus intensity is suitably adjusted. On the other hand, the obvious dissociation between the H reflex and W_2 shown by the recruitment curve of the lumbosacral response and the EMG (i.e., H and M) responses, as well as by the H-H conditioning experiments, allowed us to exclude conclusively any contribution of the ventral root volley to the W_2 component. This confirms the original view of El Negamy and Sedgwick (1978). Instead, it seems most likely that W_2 is due to the spreading of the S wave (or, most probably, of its postsynaptic component), as suggested by their simultaneity, spatial distribution and polarity changes at the thoracolumbar junction. A similar hypothesis was advanced by Jones and Small (1978), their 'fixed large amplitude lower thoracic-lumbar response' apparently corresponding to the S wave. While there is little doubt that the latter is mainly generated by spinal structures under synaptic influence (in fact, the S wave can be recorded from the cord segments receiving tibial nerve afferents, that is, L5, S1 and S2, which are situated very close to the T12 vertebra), the evidence so far available does not permit a decision as to what extent long and/or short axon spinal neurons are respectively involved in its origin.

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PERIPHERAL NEUROPATHY IN TANGIER DISEASE

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SUMMARY

Peripheral nerve morphometry was assessed in four patients with Tangier disease. Three patients with a relapsing and remitting multiple mononeuropathy had prominent peripheral nerve demyelination and remyelination with affected internodes clustered along particular nerve fibres. Putative lipid vacuoles were almost exclusively confined in this multifocal neuropathy syndrome to Remak cells. By contrast a fourth patient with a slowly progressive syringomyelia-like neuropathy had advanced peripheral nerve degeneration and a more global distribution of lipid vacuoles within peripheral nerve. A review of Tangier disease in the literature indicated the possibility of additional peripheral nerve syndromes. The clinical heterogeneity raises the possibility of different metabolic errors in Tangier disease or a common metabolic error subject to genetic influences. The results of this study indicate that normal serum cholesterol levels do not exclude a diagnosis of Tangier disease. It is therefore advisable to determine both high density lipoproteins and serum cholesterol levels in patients with undiagnosed multifocal neuropathy or syringomyelia-like syndromes.

INTRODUCTION

Tangier disease is a rare familial disorder characterized by a near absence of normal high density lipoproteins (HDL) (Fredrickson *et al.*, 1961) and their major protein constituents, apolipoproteins (apo) A-I and A-II (Schaefer *et al.*, 1981). Tangier disease may have its course complicated by one of two distinct neurological syndromes. The first syndrome is a slowly progressive symmetrical neuropathy with a syringomyelia-like distribution (proximal dissociated sensory loss and facio-brachial muscle wasting and weakness). The second syndrome is a multifocal neuropathy which may show striking remissions. It has always seemed unlikely that the same pathological process in Tangier disease could underlie two such contrasting peripheral nerve syndromes (Kocen *et al.*, 1973). However, quantitative peripheral nerve studies have been previously reported only in the slowly progressive syringomyelia-like neuropathy of Tangier disease (Kocen *et al.*, 1973; Dyck *et al.*, 1978). In this study morphometric peripheral nerve findings in three cases of Tangier disease with asymmetrical fluctuating neuropathies are compared with those found in a case with a syringomyelia-like presentation. The opportunity has also been taken to review critically the manifestations of peripheral neuropathy in Tangier disease.

CASE REPORTS

Case 1

A 21-year-old Caucasian female was one of five children from a nonconsanguineous marriage. She had had an uneventful early life until at the age of 16 years she developed winging of the right scapula which resolved after several months. When aged 18 years she noted progressive weakness of both ankles, particularly the left, and subsequently weakness of the hips and later of the left hand. Examination showed asymmetrical limb weakness, most marked distally in the left arm. There was no muscle wasting or fasciculation. The biceps reflexes were present but all other tendon reflexes absent. There was minimal diminution of pain sensation symmetrically in the fingers and toes without impairment of light touch, pin prick, vibration or position sense. Cerebrospinal fluid examination was normal. She was treated empirically with prednisone and azathioprine. There was marked improvement of muscle strength over the ensuing four weeks but subsequently she deteriorated when treatment was withdrawn because of side effects. Plasmapheresis at 19 years of age (6 3l exchanges) and a trial of cyclophosphamide one year later had no clinical effect. At the age of 21 years she developed right wrist drop and right hand weakness and at times her legs became so weak she needed a wheelchair. At about this time she became troubled by persistent numbness and tingling in the hands and feet.

Examination showed that the posterior pharyngeal wall and tonsillar fossa contained small yellow pigmented follicles. There were no skin lesions, lymphadenopathy, hepatosplenomegaly or corneal infiltration. Cognitive function and cranial nerve examination were normal. There was severe wasting and weakness of intrinsic muscles of the right hand, and right wrist extension was paralysed. Moderately severe weakness of elbow and knee extension and of ankle dorsiflexion was present bilaterally. Only the biceps tendon reflexes were present. There was sensory diminution of all modalities in a glove and stocking distribution shading to normal in the midforearms and midcalves, respectively. Tests for postural hypotension, cold pressor response and the valsalva reflex were normal.

Electromyography of affected distal muscles showed a moderate reduction in the number of motor unit potentials on maximum voluntary effort and an increase in motor unit firing rates. Nerve conduction studies revealed prolongation of sensory action potential latencies in the median and ulnar nerves with focal slowing of motor conduction in the left ulnar nerve at the elbow (Table 1).

At the age of 22 years she improved symptomatically and was able to resume voluntary work and horse riding.

A whole right sural nerve biopsy was performed under local anaesthesia in June 1981.

Case 2

The 26-year-old brother of Case 1 had an eleven year history of fluctuating limb weakness. He had had tonsillectomy and adenoidectomy when aged 5 years with adenoidectomy repeated on two further occasions. Unexplained intermittent diarrhoea had occurred during infancy.

At the age of 15 years he complained of progressive weakness and numbness of the left leg for several months. Neurological examination showed minor weakness of the intrinsic muscles in both hands together with wasting and weakness in both legs, most marked in the left foot. Moderately severe weakness of the left leg and foot persisted for four years and then completely resolved over several months. At 25 years of age he again became symptomatic with slight weakness of left wrist extension and of hand grip bilaterally.

Examination revealed yellow tonsillar remnants and small yellow pharyngeal follicles. There was minor splenomegaly but no hepatomegaly, lymphadenopathy or corneal infiltration. An early systolic click and late systolic murmur were heard at the apex. Cranial nerves and cognitive function were normal. There was minor weakness of left wrist extension and left elbow flexion and of finger abduction bilaterally. Marked wasting of intrinsic foot muscles was associated with minimal weakness of toe flexion bilaterally (left more than right) and slight weakness of right ankle dorsiflexion. The ankle reflexes were diminished but all other tendon reflexes were normal. Light touch, pain, temperature, vibration and position sense were all slightly impaired in the toes. Nerve conduction studies demonstrated prolonged distal sensory latencies (Table 1).

A whole left sural nerve bipsy was performed under local anaesthesia at the midcalf and ankle levels in September 1981.

Case 3

The 19-year-old brother of the two previous cases had intermittent unexplained diarrhoea as a child and tonsillectomy had been performed at 6 years of age.

At the age of 12 years he gradually developed weakness in both legs. After two years he was unable to run, jump or to stand readily from a squatting position. He noted progressive wasting of the left leg during the next two years. At the age of 16 years all symptoms resolved over three months. One year later he developed marked weakness of the left arm over several weeks and though there was subsequent improvement, weakness at the left elbow persisted. When aged 18 he became progressively weaker in both ankles and dragged his toes while walking. This was associated with numbness of both feet.

On examination yellow follicles were observed in the posterior pharynx and tonsillar fossa. Lymph nodes were not enlarged but there was minor enlargement of the liver and spleen. A yellow pericorneal infiltrate was seen on slit-lamp examination. Mentation and cranial nerve function were normal. There was severe wasting of the left biceps, moderate wasting of triceps and deltoid muscles and minor wasting of the left forearm and intrinsic muscles in both feet. Weakness was most marked in the left arm and hand with minor weakness of handgrip on the right. There was moderate weakness of left ankle dorsiflexion and eversion and of right plantar flexion. Only the triceps reflexes were present. Light touch, pain, temperature, vibration and position sense were all slightly impaired in the feet.

Electromyography of proximal muscles in the upper and lower limbs showed a moderate reduction in the number of motor unit potentials on maximum voluntary effort and an increase in motor unit firing rates. Motor units were increased up to 10 mV in amplitude. Nerve conduction studies were normal (Table 1) apart from an increased distal motor latency in the left common peroneal nerve.

A whole left sural nerve biopsy was performed at the midcalf and ankle levels under local anaesthesia in September 1981.

Case 4

Detailed clinical (Haas *et al.*, 1974) and sural nerve morphological findings (Kocen *et al.*, 1973) of this patient with Tangier disease have been previously reported. He is unrelated to Cases 1-3. He was born in 1920 and at the age of 22 years noted symmetrical wasting and weakness of the hands and shoulders. This slowly progressed to a widespread generalized loss of pain and temperature appreciation which spared only the distal parts of the legs. Weakness of eye closure followed. In 1969 he developed severe sharp paroxysmal pains involving multiple sites on his body. The attacks of lancinating pain have continued two to three times per month, each lasting up to 36 h. Initially troubled by excessive sweating, in 1979 he became anhidrotic except in the neck region. He has had no postural hypotension, bladder disturbance or impotence and with dogged determination is still able to drive a car, garden and work a hand letterpress.

Positive findings on neurological examination in 1982 included a global loss of light touch, pain and temperature. Joint position and vibration sense were only slightly impaired distally in the extremities. He had gross wasting and weakness of the face, arms and hands, but normal power in the legs. Fasciculations were prominent in the limbs associated with areflexia and flexor plantar responses. There was electrophysiological evidence of severe chronic denervation in proximal and distal limb muscles. Median, ulnar and sural sensory action potentials were absent and no motor response

TABLE 1 NERVE CONDUCTION STUDIES IN PATIENTS WITH TANGIER DISEASE

			Sensory conduction				*Motor conduction*					
			Median		*Sural*		*Median*			*Ulnar*		
Patient	*Age (yrs)*	*Year*	*Latency*[1] *(ms)*	*Amplitude*[2] *(μV)*	*CV*[3] *(m/s)*	*Amplitude (μV)*	*CV*[4] *(m/s)*	*Latency*[5] *(ms)*	*Amplitude mV*	*CV (m/s)*	*Latency (ms)*	*Amplitude (mV)*
Case 1	17	1978	4.0	30	29	10	51	5.6	7	55	3.8	10
	20	1981	2.9	40	46	4	—[6]	—	—	56	2.6	10
Case 2	26	1981	3.7	15	33	8	48	4.6	5	47	3.3	12
Case 3	16	1979	2.9	40	—	—	54	4.2	5	—	—	—
	18	1981	3.1	20	40	10	52	3.6	4	60	3.1	8
Case 4	61	1982	0[7]	0	0	0	0	0	0	0	0	0
Control												
Mean			2.8	27	49	19	59.1	3.4	10.7	59.8	2.7	11.1
Range			2.1–3.5	13–51	42–56	6–47	49–74	2.5–4.6	3.7–21.4	47–72	1.6–4.2	5.6–20.8

[1] Stimulus artefact to peak of sensory action potential. [2] Amplitude of maximal negative deflection. [3] Peak-to-peak conduction velocity between midcalf and ankle (14 cm). [4] Conduction velocity of fastest conducting (elbow-wrist) fibres. [5] Stimulus artefact to take off of motor action potential. [6] Indicates EMG study not performed. [7] No response

was obtained from stimulation of median, ulnar, common peroneal and anterior tibial nerves (Table 1).

Biopsies of the whole left and right sural nerves were performed in 1971 and 1982, respectively.

Other Investigations

Serum lipids in the four patients are seen in Table 2. Extensive lipid analyses in Cases 1–3 (Frith *et al.*, 1982) demonstrated an absence of apo A-I. Cholesterol levels were within the normal range in Cases 1 and 3 because of inheritance of both Tangier disease and the heterozygous state for combined hyperlipidaemia. Negative or normal laboratory tests included full blood count, sedimentation rate, urinalysis, serum urea and electrolytes, serum glutamic oxaloacetic acid transaminase, lactic dehydrogenase and creatine kinase, serum total protein, serum protein electrophoresis and immunoglobulins (IgG, IgA and IgM), fasting blood sugar, urinary porphyrins, serum and urinary lead, ANA tests, serum vitamin B_{12}, serum folate, CSF, ECG, EEG. Congo red staining for amyloid was negative in all nerve biopsies.

TABLE 2. SERUM LIPID FINDINGS IN TANGIER PATIENTS AND CONTROLS

Patient	*Sex*	*Age (yrs)*	*Serum cholesterol (mmol/l)*	*Serum triglyceride (mmol/l)*	*HDL*[1] *cholesterol (mmol/l)*
Case 1	F	20	4.6	2.7	< 0.2
Case 2	M	26	1.9	1.4	< 0.2
Case 3	M	18	3.6	2.0	< 0.2
Case 4	M	60	0.9	5.93	0.1
Controls			3.0–7.5	< 2	0.6–2.0

[1] High-density lipoproteins.

METHODS

Whole sural nerve biopsies were obtained under local anaesthesia at the ankle level from the four Tangier patients. An additional sural nerve specimen was obtained at the midcalf level in Cases 2 and 3. Human control sural nerve had been previously obtained from nine unpaid volunteers who had given informed consent (Declaration of Helsinki) after normal neurological evaluation and normal nerve conduction studies.

Sural nerve specimens were fixed initially in 2 per cent glutaraldehyde in 0.1 M cacodylate buffer (pH 7.40) at room temperature, followed by 1½ h in 1 per cent osmium tetroxide in the same buffer. The portion of nerve for teasing in glycerol was fixed in glutaraldehyde for 10 to 15 min while segments for epoxy embedding were fixed for 1½ to 2 h in glutaraldehyde.

One hundred single teased nerve fibres, with a minimum of four internodes, were sought from each sural nerve. Teased fibres were graded descriptively as: A, normal appearance; B, marked irregularity of myelin; C, segmental demyelination; D, segmental demyelination and remyelination as evidenced by at least a 50 per cent reduction in myelin thickness; E, linear rows of myelin ovoids; F, segmental remyelination with internodes showing 50 per cent or more difference in myelin thickness; G, focal irregularity of myelin forming globules or 'sausages', and H, myelin ovoids contiguous to two or more thinly myelinated internodes (Pollock and Dyck, 1976). In the analysis of internodes a χ^2 test was used to determine whether abnormal internodes were randomly distributed or clustered along particular nerve fibres.

Photographic enlargements of transverse epoxy sections were used for determining the number and diameter of myelinated nerve fibres per mm^2 of transverse fascicular area and per whole nerve.

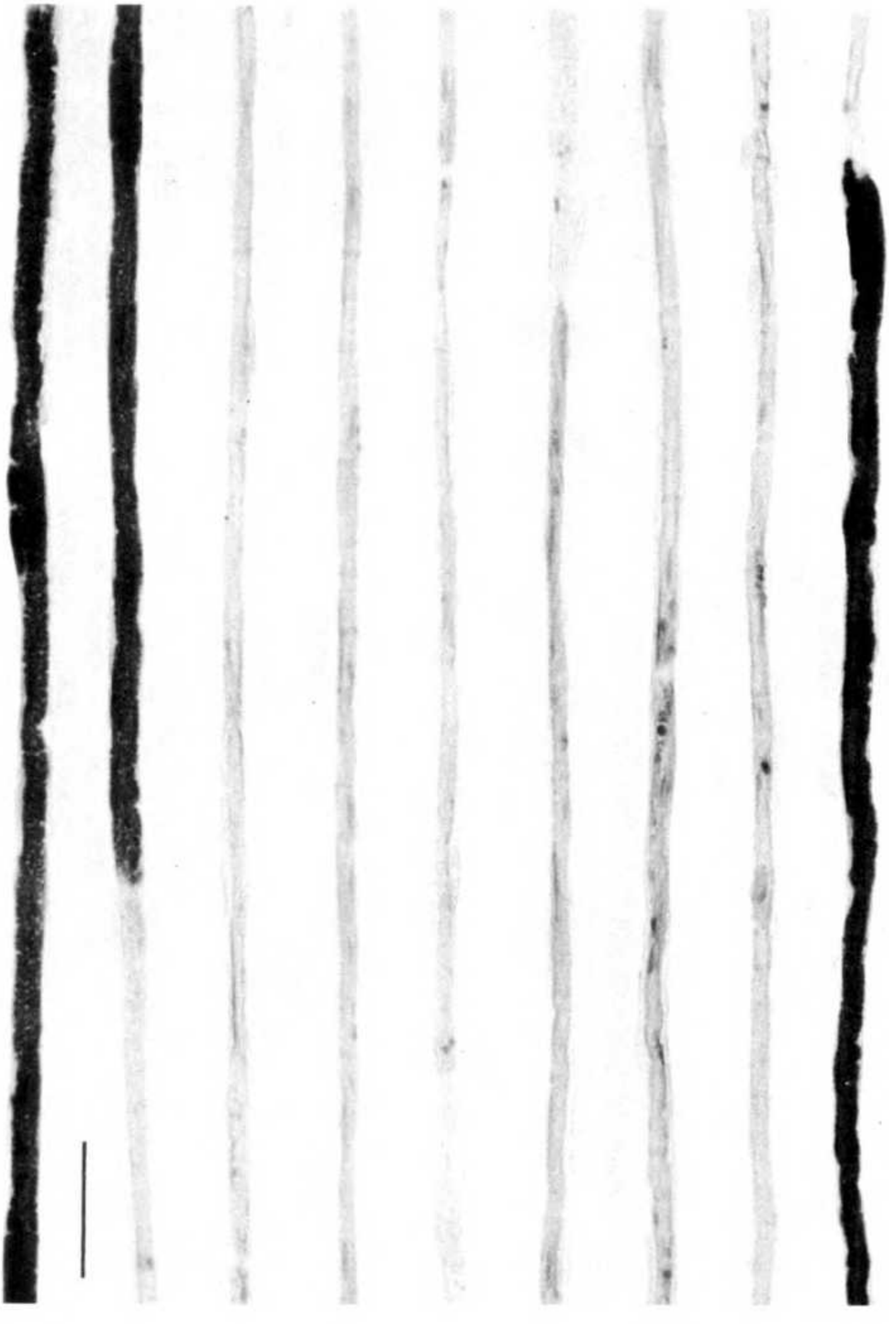

FIG. 1. *Case 1.* A teased nerve fibre from a patient with Tangier disease and a multifocal neuropathy showing consecutive remyelinated internodes and a demyelinated segment (Type D) in the fifth strip extending into the sixth. Bar = 40 μm.

Densities were calculated for all nerve fibres as well as for small (diameter $\leqslant 7.05\ \mu m$) and large (diameter $> 7.05\ \mu m$) myelinated fibres. Diameter histograms were then determined using programmed calculation and plotting. For each nerve, unmyelinated fibres in 35 to 40 electron micrographs (area $\geqslant 0.015\ mm^2$) were counted and measured with a particle size analyser (Zeiss TGZ-3) set on a linear scale. On the same photographic enlargements, numbers of collagen pockets, Schwann cell, fibroblast and macrophage nuclei were also determined. The distribution of both myelinated and unmyelinated nerve fibre diameters was compared with that of controls using the Kolmogorov-Smirnov 2-sample test (Siegel, 1956).

RESULTS

Multiple Mononeuropathy Syndrome (Cases 1-3)

Teased sural nerve fibres at ankle level from the three Tangier patients with a multifocal neuropathy showed a significant increase ($P < 0.005$) of demyelinated (type C) and remyelinated internodes (type D, F) but no increased incidence of degenerating fibres (type E) (Table 3, fig. 1). Case 3 had a similar frequency of demyelinated and remyelinated internodes at the ankle and midcalf level. The fixation of teased nerve fibres from Case 2 at the midcalf level was inadequate for proper assessment. A χ^2 analysis of the distribution of demyelinated and remyelinated internodes indicated a nonrandom distribution of affected internodes ($P < 0.001$).

TABLE 3. GRADING OF TEASED MYELINATED FIBRES IN SURAL NERVES OF PATIENTS WITH MULTIPLE MONONEUROPATHY IN TANGIER DISEASE

		Graded pathological abnormalities (%)[1]								
Patient	*Biopsy site*	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*Abnormal* (%)
Case 1	Ankle	35	0	18	29	2	16	0	0	65
Case 2	Ankle	21	0	4	31	1	42	0	1	79
Case 3	Ankle	76	0	5	3	1	15	0	0	24
	Midcalf	79	0	0	4	2	15	0	0	21
Control mean	Ankle[2]	92	0	0.1	0.1	0.8	7	0	0	8

[1] *See* text for explanation of fibre types. [2] n = 9 nerves.

Transverse sections of sural nerve at the ankle level showed normal numbers of myelinated fibres per mm² of fascicular area (Table 4, fig. 2A). Case 1 with fascicular atrophy (Table 4) had a reduced number of myelinated nerve fibres (4415) per whole nerve. Myelinated fibre diameter histograms for Tangier patients were significantly different compared with controls by the Kolmogorov-Smirnov test ($P < 0.001$), due to a reduction in the large fibre peak and an increase in the small fibre category (fig. 3). Tangier patient mean nerve diameters for total and large fibres (Table 5) were significantly reduced ($P < 0.001$) compared with controls. Densities of

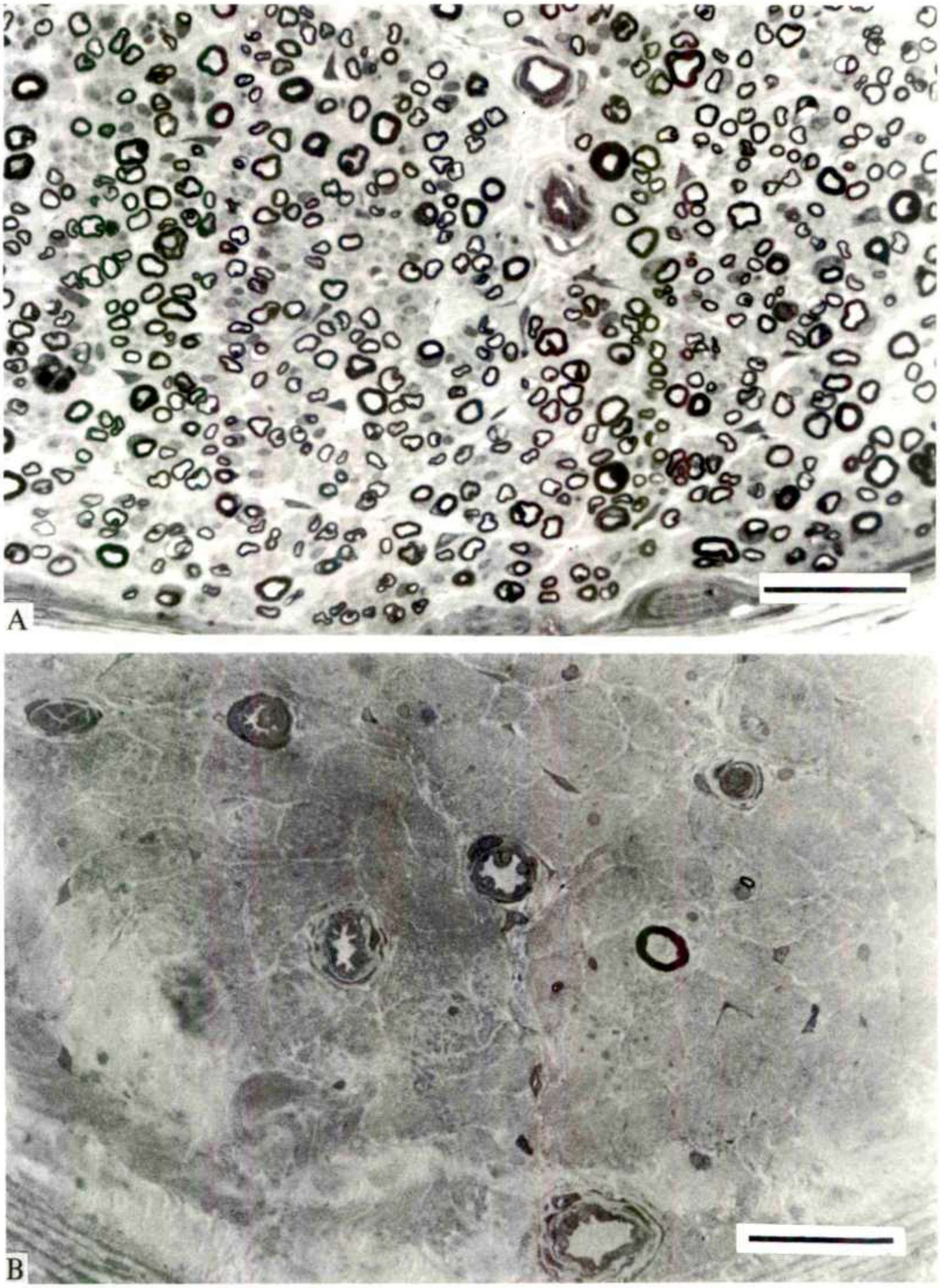

FIG. 2A. Transverse section of sural nerve from *Case 1* with Tangier disease and a multifocal neuropathy demonstrating a normal myelinated nerve fibre density. The diameter distribution of myelinated nerve fibres is abnormal due to an excessive number of small myelinated fibres. B, transverse section of sural nerve from *Case 4* with Tangier disease and a syringomyelia-like neuropathy showing a virtual absence of myelinated nerve fibres. Bar = 40 μm.

myelinated sural nerve fibres at the midcalf level in Cases 2 and 3 were 10 454/mm^2 and 12 199/mm^2, respectively.

Groups of unmyelinated fibres in osmium stained transverse sections had a characteristic golden hue by light microscopy. Longitudinal peripheral nerve sections revealed long rows of small clear or osmiophilic vacuoles. Electron microscopy showed that not all vacuoles were membrane bound and they were preferentially located in Remak cells (fig. 4A). Unmyelinated axons adjacent to vacuoles usually appeared normal. In an assessment of 500 Remak cells in each nerve biopsy specimen, the incidence of cytoplasmic vacuoles varied between 22–54 per cent of cells (Table 6). The incidence of vacuoles within Remak cells was greater distally in Case 2 but not in Case 3 (Table 6). A similar assessment of 500 myelinated nerve fibres in each biopsy specimen revealed a total of only 4 Schwann cells with cytoplasmic lipid vacuoles (Table 6). Vacuoles were infrequently present in fibroblasts (fig. 4B) and in perineurial cells (fig. 4C) and were not present in endoneurial endothelial cells or within axons.

TABLE 4. TOTAL FASCICULAR AREA, NO. OF FASCICLES AND NO. OF MYELINATED AND UNMYELINATED FIBRES OF SURAL NERVES IN PATIENTS WITH TANGIER DISEASE

Patient	*Syndrome*	*Fascicular area (mm²)*	*No. of fascicles*	*No. of fibres/mm²*	
				Myelinated	*Unmyelinated*
Case 1	MM[1]	0.52	6	8475	22163
Case 2	MM	0.94	8	7262	18120
Case 3	MM	0.63	9	11252	17400
All MM patients		0.70[2] ± 0.22		8996 ± 2045	19228 ± 2567[3]
Case 4	PS[4]	0.45	9	20	156
Controls[5]		0.84 ± 0.21	8.4 ± 1.6	7812 ± 1630	26719 ± 3729

[1] Multiple mononeuropathy. [2] Mean ± SD. [3] $P < 0.01$. [4] Pseudosyringomyelia. [5] n = 9 nerves.

Multivesicular lesions were also present in myelinated nerve fibres principally located immediately external to the axolemma or within the myelin sheath. They were also infrequently seen in Remak cells, fibroblasts and lying free within the endoneurium (fig. 5). There was no evidence of active axonal degeneration or macrophage infiltration.

Quantitative electron microscopy revealed significantly reduced densities ($P < 0.01$) of unmyelinated nerve fibres in the three Tangier nerve biopsies (Table 4). Unmyelinated diameter histograms showed a significant shift ($P < 0.001$) to the left (fig. 3) and a significant reduction in total and large fibre mean diameters ($P < 0.001$). Unmyelinated nerve fibre densities at the midcalf level in Cases 2 and 3 were, respectively, 33280/mm^2 and 25638/mm^2. The mean number of myelin lamellae was significantly reduced in the sural nerves of Tangier patients with multifocal neuropathy compared with controls ($P < 0.001$) with no significant difference in axonal areas or in indices of axonal circularity (Table 7). The regression

TABLE 5. MEAN NERVE FIBRE DIAMETERS OF SURAL NERVES IN THE MULTIPLE MONONEUROPATHY SYNDROME OF TANGIER DISEASE

Patient	*Myelinated fibre diameters (μm)*			*Unmyelinated fibre diameters (μm)*		
	Small[1]	*Large*[2]	*Total*	*Small*[3]	*Large*[4]	*Total*
Case 1	4.31 ± 1.0[5]	8.74 ± 1.13	5.03 ± 1.95	0.72 ± 0.21	1.22 ± 0.07	0.76 ± 0.25
Case 2	4.26 ± 1.07	7.90 ± 0.61	4.46 ± 1.33	0.78 ± 0.22	1.23 ± 0.12	0.86 ± 0.27
Case 3	4.09 ± 1.17	9.00 ± 1.19	5.65 ± 2.57	0.86 ± 0.17	1.28 ± 0.14	0.95 ± 0.24
All patients	4.23 ± 1.10	8.81 ± 1.17[6]	5.05 ± 2.07[6]	0.77 ± 0.21	1.24 ± 0.12[6]	0.84 ± 0.26[6]
Controls	4.30 ± 1.31	10.62 ± 2.02	6.78 ± 3.49	0.79 ± 0.24	1.39 ± 0.22	1.10 ± 0.37

[1] < 7.0 μm. [2] $\geqslant 7.0$ μm. [3] < 1.08 μm. [4] $\geqslant 1.08$ μm. [5] ±SD. [6] $P < 0.001$.

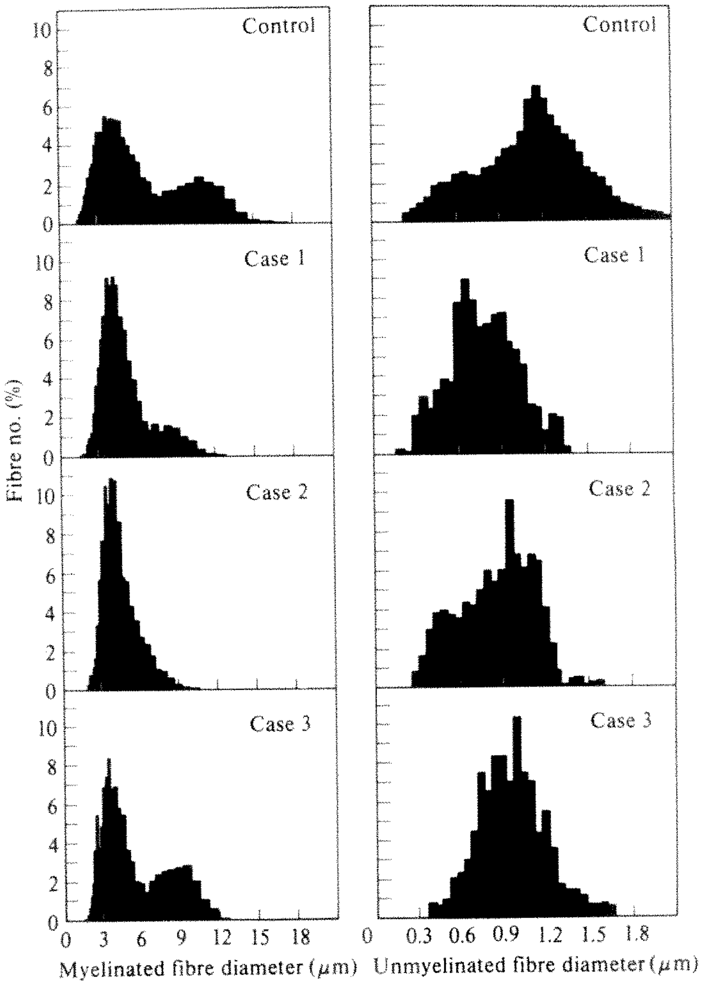

FIG. 3. Diameter histograms of myelinated and unmyelinated sural nerve fibres from Tangier patients and controls.

TABLE 6. FREQUENCY (%) OF LIPID VACUOLES PER CYTOPLASMIC PROCESS IN SURAL NERVE OF TANGIER PATIENTS

Patient	*Biopsy site*	*Remak cells*	*Myelinated fibre Schwann cells*	*Fibroblasts*	*Perineurial cells*	*Endothelial cells*
Case 1	Ankle	54	0.01	3	2	0
Case 2	Ankle	45	0.01	4	3	0
	Midcalf	7				
Case 3	Ankle	22	0.1	0	0	0
	Midcalf	26				

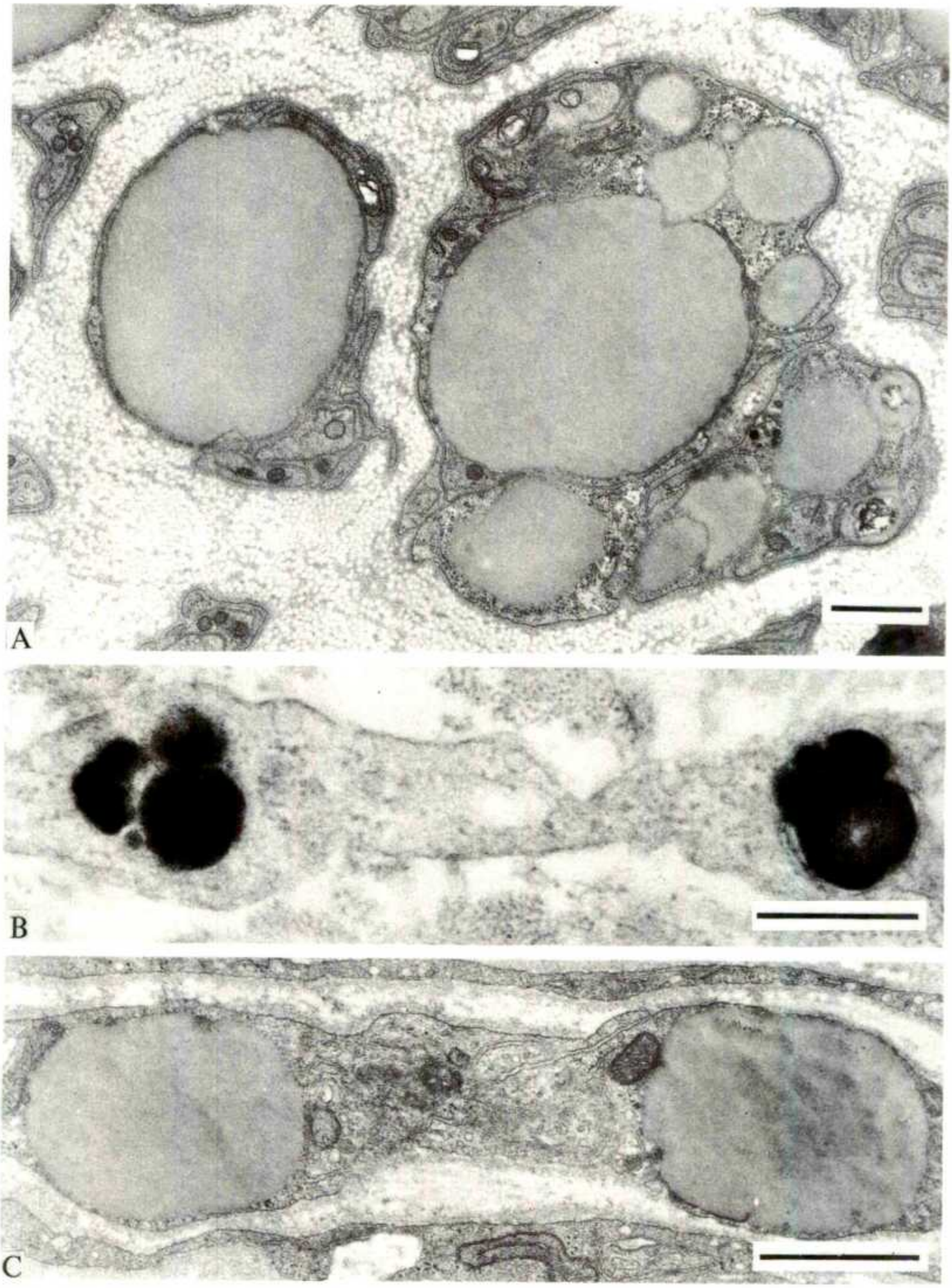

FIG. 4. *Case 1*. Electron micrographs of transverse sections of sural nerve. A, multiple membrane-bound lipid vacuoles in the cytoplasm of Remak cells. The quantity of endoneurial collagen is excessive. Bar = 1.0 μm. B, osmiophilic vacuoles in a fibroblast. Bar = 0.5 μm. C, lipid vacuole formation within the perineurium. Bar = 1.0 μm.

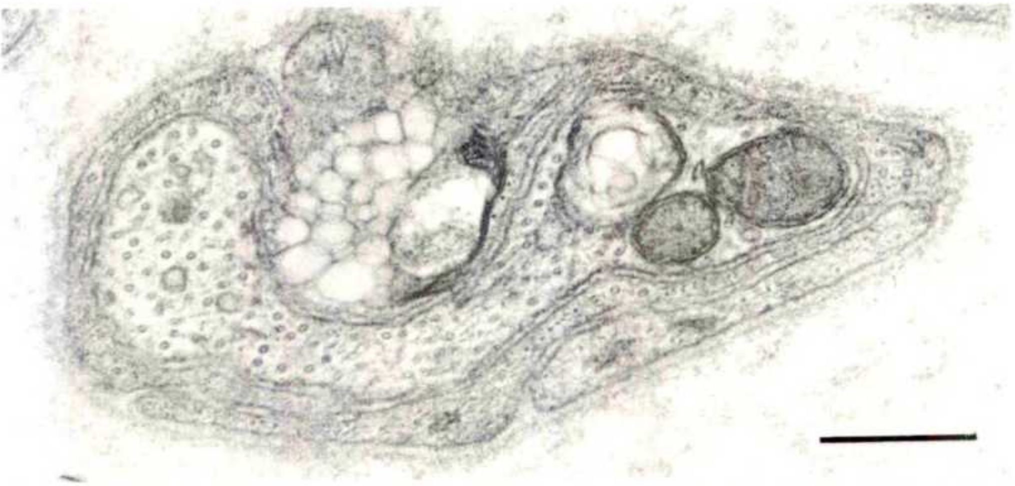

FIG. 5. Electron micrograph of transverse section of sural nerve from *Case 2* showing multiple vesicle formation in the cytoplasm of a Remak cell. Bar = 0.5 μm.

line for axonal area *vs* number of myelin lamellae for the nerves of Tangier patients was significantly separated ($P < 0.001$) from that for controls (fig. 6). This also suggested a reduced number of myelin lamellae in Tangier patient nerve. There was no statistically significant increase in densities of collagen pockets or in Schwann cell, fibroblast or macrophage nuclei in the three Tangier patients with multifocal neuropathy (Table 7).

Pseudosyringomyelic Syndrome (Case 4)

Transverse sections of the right whole sural nerve at the ankle in Case 4 with Tangier disease and a symmetrical syringomyelia-like neuropathy, showed only 9 myelinated fibres per whole nerve with extensive endoneurial collagen formation (fig. 2B). The sural nerve transverse fascicular area measured only 0.45 mm².

The left sural nerve, removed eleven years previously, had contained 10 myelinated fibres per whole nerve. It was not possible to tease out any individual

TABLE 7. QUANTITATIVE VALUES OF SURAL NERVES IN PATIENTS WITH TANGIER DISEASE

Patient	*Syndrome*	*Nuclei/mm²* *Schwann*	*Fibroblast*	*Macrophage*	*Collagen pockets (per mm²)*	*Myelinated fibres* *No. of lamellae*	*Axonal area*	*Axonal IC*[1]
Case 1	MM[2]	1599	305	0	2589	54 ± 29[3]	9.5 ± 8.7	0.796 ± 0.10
Case 2	MM	1806	498	62	1681	40 ± 27	9.8 ± 7.5	0.859 ± 0.08
Case 3	MM	1465	410	0	1582	57 ± 33	10.9 ± 7.4	0.842 ± 0.09
All MM patients		1623 ± 172	404 ± 97	21 ± 36	1951 ± 555	50 ± 31	10.1 ± 7.9	0.833 ± 0.09
Case 4	PS[4]	466	933	0	104			
Controls		2452 ± 667	273 ± 135	28 ± 38	3633 ± 1671	58 ± 33	9.4 ± 9.2	0.823 ± 0.17

[1] Index of circularity = $\frac{2\sqrt{\pi a}}{P}$ where a = area and P = perimeter (Dyck *et al.*, 1980). [2] Multiple mononeuropathy. [3] Mean ± SD. [4] Pseudosyringomyelia.

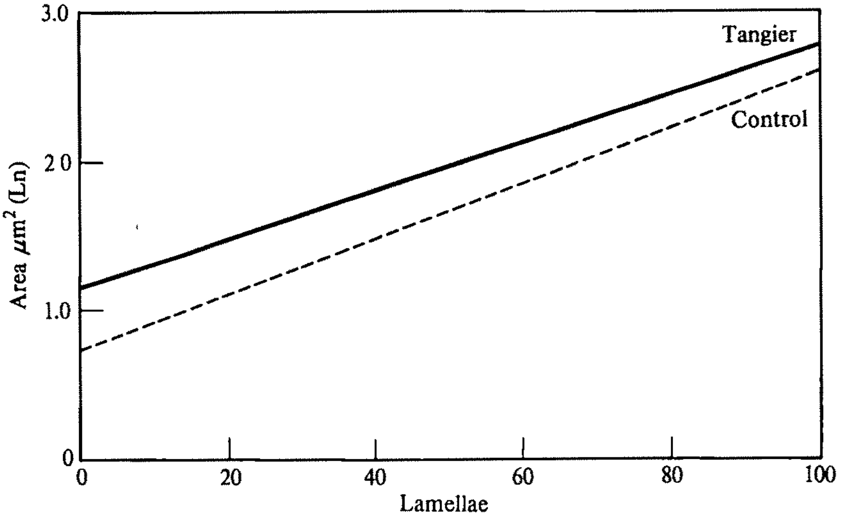

FIG. 6. Mean regression lines for axonal area (log to base e) and number of myelin lamellae in sural nerve biopsies from patients with Tangier disease and multiple mononeuropathy (solid line) and controls (broken line)

myelinated nerve fibres from the present biopsy. The unmyelinated nerve fibre density was also strikingly reduced (Table 4). Putative lipid vacuoles closely resembled those seen in the multifocal neuropathy form of Tangier disease. They were not all membrane bound and were present in the cytoplasm of the few remaining myelinated and unmyelinated fibres and within fibroblasts, perineurial, endothelial and mast cells. The reduced Schwann cell population (Table 7) showed marked proliferation of endoplasmic reticulum and reduplication of basement membrane. Prominent pinocytotic vesicle formation was seen in Schwann cells, fibroblasts, endothelial cells and pericytes.

DISCUSSION

With age, neuropathy becomes an increasingly frequent complication of Tangier disease. Including the 3 cases with a multiple mononeuropathy in this study, peripheral neuropathy has been present in 16 of 30 patients with Tangier disease (Herbert *et al.*, 1978; Suarez *et al.*, 1982). In the following discussion, patients with case numbers enclosed in square brackets refer to those categorized in order of publication by Herbert *et al.* (1978). There is no unequivocal evidence that case [14] had a neuropathy while it is now clear that case [26] manifests a syringomyelia-like neuropathy (Brook *et al.*, 1977). Thus 16 of 21 adult patients so far identified with Tangier disease have had peripheral nerve involvement (Schaefer *et al.*, 1980). Moreover, in some adult patients with weakness a detailed neurological examination has not been reported to exclude convincingly peripheral neuropathy (Suarez *et al.*, 1982). Abnormal peripheral nerve histology has also been documented in Tangier disease when neurological examination, quantitative tests of cutaneous sensation and nerve conduction studies were normal (Dyck *et al.*, 1978). Whenever sural nerve biopsy is contemplated in Tangier patients it needs to be preceded by a haematological evaluation because of the risk of an associated bleeding disorder (Bale *et al.*, 1971; Schaefer *et al.*, 1980).

Peripheral neuropathy in Tangier disease has manifested as a syringomyelia-like syndrome in four cases [7, 13, 25 and 26] (Table 8). An initial sensory loss for pain in the face, arms and upper trunk has been followed by a symmetrically progressive faciobrachial wasting and weakness. Clinically and pathologically the neuropathy has always been most marked in the arms with a predominantly early involvement of the small myelinated and unmyelinated fibres (Dyck *et al.*, 1978). Progressive autonomic involvement has been reflected by increased sweating and later anhidrosis. The varied age of clinical onset of the neuropathy has been inversely related to the subsequent course. Thus the time to neurological disability in case [25] with onset at the age of 51 years was 5 years, while that of case [13] with onset at 22 years was 25 years. Attacks of stabbing pain have suggested involvement of dorsal root ganglion cells (Haas *et al.*, 1974), but to date neither dorsal root ganglia nor anterior horn cells have been examined.

TABLE 8 CLINICAL CHARACTERISTICS AND PATHOLOGICAL FEATURES OF THE TWO COMMON PERIPHERAL NERVE SYNDROMES IN TANGIER DISEASE

	Pseudosyringomyelic neuropathy	*Multiple mononeuropathy*
Onset (decades)	3–6	1–2
Inheritance	Autosomal recessive	Autosomal recessive
Pathology	Axonal degeneration	Demyelination-remyelination
Early fibre loss	Small MF[1] + UF[2]	UF
Lipid inclusions	All cells	Remak cells
Initial weakness	Facio-brachial	Isolated peripheral nerve(s)
Sensory loss		
Early	Dissociated[3]	Not dissociated
Late	All modalities: centrally	All modalities: distally
EMG		
Denervation	+++	+
SPA[4]	0[5]	N[6]
Latencies	N	↑
Blood lipids		
Cholesterol	↓	N or ↓
HDL[7]	↓	↓
Triglyceride	N or ↑	N or ↑
Course	Progressive	Relapsing-remitting
Prognosis	Disability	Benign

[1] Myelinated fibre. [2] Unmyelinated fibre. [3] Initial pain and temperature impairment. [4] Sensory potential amplitude. [5] Unrecordable. [6] Normal. [7] High-density lipoproteins.

With the present report a total of 7 patients with Tangier disease have had a symptomatic multifocal neuropathy, including cases [1, 2, 8 and 9] (Table 8). Isolated palsies of oculomotor, trunk and limb nerves have all been reported. The most striking feature has been exacerbations of neuropathy lasting up to two years in duration. With severe attacks there has been weakness in all limbs with proximal or distal accentuation. Sensory loss has usually involved all modalities in a glove and stocking distribution. To date all patients have slowly recovered from such episodes but in two instances recovery appeared to be related to the initiation of steroid treatment.

Neuropathy in the remaining cases [4, 5, 10, 18 and 21] with Tangier disease has varied in its clinical manifestations. Some who may yet develop a typical picture of relapsing multiple mononeuropathy have had only mild asymmetrical weakness and depressed stretch reflexes. In other patients with Tangier disease the neuropathy has not conformed to either of the typical syndromes. Thus case [20] developed a painful proximally accentuated axonal polyneuropathy with bilateral stocking anaesthesia (Hager and Zimmermann, 1979). Its onset and rapid progression in the sixth decade necessitated premature retirement.

The basis for this clinical heterogeneity remains obscure. From a study of two separate families, Schaefer *et al.* (1982) proposed a structural defect in apo A-I as the primary abnormality in Tangier disease. Possibly there may exist variant 'Tangier forms' of apo A-I, reflecting an underlying genetic heterogeneity or the same abnormal apolipoprotein might in different individuals interact in different ways with other lipoprotein fractions (Alaupovic *et al.*, 1981) with modulation of its end-effect. Alternatively, there might exist normal variation at the level of peripheral nerve such that its response to the metabolic insult differs. Thus in particular Tangier families pathology might predominate either proximally in dorsal root ganglia and anterior horn cytons and result in a slowly progressive symmetrical neuropathy or distally in Schwann cells to produce a multiple mononeuropathy.

Nerve biopsies from the three patients with Tangier disease and asymmetrical fluctuating sensorimotor neuropathies in this study had a high incidence of demyelinated and remyelinated peripheral nerve fibres with an overall significant reduction in myelin lamellae. This morphological finding provides a pathological basis for the remissions and exacerbations of multifocal neuropathy in Tangier disease. By contrast there is prominent axonal degeneration but no evidence of demyelination or remyelination in the syringomyelia-like neuropathy of Tangier disease (Kocen *et al.*, 1973; Dyck *et al.*, 1978).

Intracytoplasmic vacuoles in the multiple mononeuropathy form of Tangier disease were almost exclusively confined to Remak cells. The storage of the presumed lipid in up to one half of Remak cells was associated with a 30 to 50 per cent reduction in unmyelinated nerve fibres. This finding contrasted with the normal density of sural nerve myelinated fibres in all three cases. Most surviving unmyelinated axons, within the processes of lipid laden Remak cells, appeared normal. Moreover, there was no clinical evidence in these present cases of autonomic dysfunction or of dissociated sensory loss. Thus although Remak cells are preferentially involved in the multifocal neuropathy syndrome of Tangier disease, the loss of associated unmyelinated axons within any cell appears to be at first selective and restricted. This focal pathology might account for the benign course of this type of neuropathy in Tangier disease.

Lipid accumulation within peripheral nerve in Tangier disease could result from a failure of cholesterol removal mechanisms (Kocen *et al.*, 1973) due to the virtual absence of plasma HDL. These lipoproteins are believed to be involved in the 'reverse transport' of cholesterol from peripheral tissues (Glomset and Norum, 1973; Reichl *et al.*, 1982) and thus the absence of plasma HDL in Tangier disease may result in augmented levels of unesterified cholesterol in peripheral nerve. An increase in unesterified cholesterol levels would in turn stimulate cholesterol esterification and lead to elevated levels of cholesteryl esters in the endoneurium. This postulate is consistent with the results of a previous study which showed increased levels of endoneurial unesterified cholesterol and cholesteryl esters in Tangier disease (Yao *et al.*, 1978). It has been proposed that cholesteryl esters may serve as a carrier and storage form for otherwise toxic free fatty acids (Ramsey, 1973). Might endoneurial cholesteryl esters therefore be formed in Tangier disease to combat a rise in fatty acid concentration following nerve degeneration? In peripheral nerve crush experiments, unlike the peripheral nerve findings in Tangier disease, unesterified endoneurial cholesterol levels decline concomitantly with an increase in cholesteryl esters (Yao *et al.*, 1980). Moreover with remyelination, levels of cholesteryl esters gradually return to normal. Normal myelinated nerve fibre densities in the present Tangier patients also make it unlikely that surplus endoneurial lipid is principally derived from nerve fibre degeneration.

In the differential diagnosis of peripheral neuropathy with hypocholesterolaemia, patients with Bassen-Kornzweig syndrome (abetalipoproteinaemia) have decreased rather than normal or mildly elevated triglyceride levels (Schaefer *et al.*, 1980). Similarly a disproportionate decrease in apo A-I relative to apo A-II differentiates patients with Tangier disease from those with severe secondary HDL deficiency and peripheral neuropathy due to paraproteinaemia or liver disease (Utermann *et al.*, 1975). It is clear from the present family with combined hyperlipidaemia and Tangier disease that normal serum cholesterol levels do not rule out Tangier disease. Assuming that the association is not unique it would seem advisable to determine both cholesterol and high-density lipoprotein levels in patients with undiagnosed asymmetrical relapsing-remitting neuropathies or syringomyelia-like syndromes.

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MICROBEHAVIOURAL ANALYSIS OF THE CHOICE REACTION TIME RESPONSE IN SENILE DEMENTIA[1]

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SUMMARY

Microbehavioural analysis of the human button-press response in a choice reaction time task enabled us to observe the traditional components of reaction time performance and also several additional indicators of psychomotor organization. The principal finding reported here is that in normal subjects stimulus conditions of varying difficulty differentially affect segments of the button-press response not ordinarily associated with cognitive demands of the task. This observation suggested the presence of a certain interaction between cognitive demands of the task and the subsequent motor output control. In a comparison of normal elderly and demented subjects, we demonstrated that the slower reaction times of the demented represent a virtual psychomotor disintegration. The apparent disintegration is interpreted as an inability of demented subjects properly to prepare, organize, and execute the response. The degree of disintegration is most evident during the motor time, which represents a transition between resting state and actual response completion.

INTRODUCTION

The reaction time (RT) literature contains numerous attempts to separate various components of the information processing sequence which culminates in the button-press response. In older studies most of these attempts were made by varying some aspects of the stimuli used or the manner in which responses were generated. More recent investigators significantly enriched the reaction time paradigm by adding electromyographic recording (Hufschmidt and Hufschmidt, 1954; Weiss, 1965; Botwinick and Thompson, 1966), recording of the evoked potentials (Morrell and Morrell, 1966; Ritter *et al.*, 1972) and statistical modelling (Sternberg, 1969). Myographic recording enabled the investigators to separate premotor and motor times (Weiss, 1965), the first presumed to be primarily an interval of cognitive processing, and the second containing the behavioural output itself. Brain recording brought out a number of observable changes preceding the response, the 'readiness

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potential' (Bereitschaftpotential of Deecke *et al.*, 1969) being probably the most prominent. In virtually all these studies, however, the response itself was operationally defined as a single unitary event.

In the recent neurophysiological literature, another behavioural measure of information processing has been used with increasing frequency, namely, the force utilized in motor output. Its measurement is particularly noteworthy in a series of studies by Evarts and his collaborators (Evarts, 1968; Evarts and Tanji, 1976; Fromm and Evarts, 1977; Evarts and Fromm, 1978), where the relationship between single cell activity and voluntary movement was investigated, as well as in studies which investigated the structure and mode of ballistic movement (Desmedt and Godaux, 1978) or closed-loop control of movement (Marsden *et al.*, 1976). Use of force as a dependent variable in motor output research provides an advantage in that it can be measured as a continuous variable. For this reason we recently examined force-related aspects of the choice reaction time performance of young and old individuals (Vrtunski and Mack, 1982). The results indicated not only that older subjects responded more slowly, but also that they used much greater force, and their responses persisted significantly longer than those of young subjects. The implication was that the efficiency of psychomotor organization diminishes with age.

In the present study our focus is on the choice reaction time (CRT) motor performance of subjects with senile dementia of Alzheimer type (SDAT). We were led to this study by the well accepted clinical description of Alzheimer's disease as a slowly progressive, diffuse cerebral disorder with primary effects on higher cortical function (memory, orientation) and characterized by psychomotor slowing (Wang, 1977; Terry, 1978). Recent studies of reaction time performance in senile subjects showed a disproportionately greater reaction time with choice than with simple RT procedures (Ferris *et al.*, 1976; Pirozzolo *et al.*, 1981). The particular questions we wished to address were: (1) whether the choice reaction time responses of demented subjects are physically similar to those of normals, or whether they represent a qualitatively different form of psychomotor output; and (2) whether the qualitative nature of responses changes with the cognitive load imposed by different CRT tasks.

In order to address these questions, we monitored forces exerted at the response buttons throughout the test session. The time preceding, during, and following the button-press was divided into five intervals. Four stimulus conditions were used, including visual and auditory presentation of both verbal and nonverbal stimuli. On the basis of previous research we predicted that variables reflecting cognitive processing (premotor time, for example) would show greater differences between demented and normal subjects than would measures reflecting the execution of the response itself (motor time, response force, etc.). Furthermore, since performance differences due to stimulus conditions would presumably reflect differences in the level of cognitive difficulty, that is, cognitive load, and since the premotor interval has been considered to encompass the decision-making stage of the CRT response, we predicted that any stimulus effects would be reflected only in variables derived from the premotor interval.

METHOD

Subjects

Thirteen subjects with the presumed diagnosis of senile dementia of Alzheimer type (SDAT) were compared with normal elderly controls. Informed consent for participation in the study was obtained from all subjects and/or their family. The Alzheimer subjects had a history of slowly progressive intellectual deterioration, with a mean duration of two and a half years. Subjects who had a history of Huntington's disease, Parkinson's disease, cerebral vascular disease, hydrocephalus, chronic alcoholism with consequent pathology such as ataxia or liver damage, encephalitis, meningitis, toxic conditions, focal neurological signs, tumours, history of cranial surgery, seizure disorder, head trauma, or major psychiatric disturbance were excluded. One SDAT subject had a history of right carotid endarterectomy. He was diagnosed as having Alzheimer's disease on the basis of neurological examination, CT scan and clinical course, showed no focal signs and otherwise met all research criteria. Of 32 dementia patients who were examined, 13 met our criteria. CT scans were available for 9 of these subjects. Of those, scans for 2 subjects were interpreted as normal, while the remaining 7 were characterized by noticeable enlargement of ventricles and/or increase in sulcal prominence.

The presence of generalized intellectual deterioration in the 13 selected subjects was confirmed by neuropsychological assessment, including the Wechsler Adult Intelligence Scale and Wechsler Memory Scale verbal subtests, Wisconsin Card Sorting test (WCST), a complex figure copy and delayed recall test (similar to Rey-Osterrieth figure), Porteus Maze test, and tests of auditory and visual sequential attention similar to the Knox Cubes and Digit Span tests. All Alzheimer subjects had verbal factor IQs of 86 or better, showed some evidence of primary memory impairment, with an attention span of 5 or fewer units on the visual nonverbal sequential attention span (Knox cubes), and 4 or fewer digits backward. Each attained 2 or fewer shifts on the WCST and a test age of 8 years or less on the Porteus. Twelve of the 13 recalled less than 30 per cent of visual-nonverbal and auditory-verbal information presented 45 min earlier. Most showed mild to moderate impairment of figure copies.

Ten of the 13 demented subjects were able to finish the complete set of choice reaction time tests (*see* Procedure). The mean age of the senile group ($n = 10$) was 68.4 (SD 10.5) years, and mean education was 11.9 (SD 2.3) years. The control group consisted of 34 community volunteers screened with a Health Questionnaire. The Health Questionnaire used for screening control subjects was designed to probe medical history and exclude any neurological or other major medical disorder. Their mean age was 65.5 (SD 5.59) years, and mean education was 12.1 (SD 5.59) years. Neither the age nor the educational differences between two groups were statistically significant.

The screening procedure of both groups included an audiometric test, and a test of cutaneous sensitivity with an aesthesiometer. The results of the audiometry test were used to adjust volume of auditory stimuli at 75 dB above the threshold. Screening for cutaneous sensitivity failed to show any difference between the two groups.

Procedure

The experimental method involved a typical two-choice reaction time procedure, except that the standard response key switches were replaced by pressure transducers whose continuous outputs were conditioned by a movement translator (components and functions of signal conditioning were described in Vrtunski and Mack, 1982). The analog signals were sampled at 500 Hz, averaged over successive eight-sample windows (producing, in effect, averages for successive 16 ms intervals), and stored by an on-line computer.

Each subject participated in 4 randomly ordered runs, one for each of the 4 types of stimulus materials, including nonverbal line drawings (Kimura figures), pictorial drawings, patterned nonverbal sounds, and spoken words. The nonverbal sounds were patterns, 770 ms long, with a variable beginning and the last 300 ms consisting of either 1 kHz monotone ('flat') or a warbled ('chirp') tone. Spoken words were one- or two-syllable nouns, of both high and low frequency (mean count 43.9), selected from Thorndike-Lorge and Kucera-Francis lists, and averaging 768 ms in length. The visual stimuli (line drawings and pictures) were projected tachistoscopically on a screen for 2.5 s maximum. Responses with shorter RT terminated the slide presentation. Digitized auditory stimuli were presented *via* a D/A converter at 12 kHz. The choice task was to decide between 'straight' and 'curved' line drawings or 'flat' and 'chirp'-like sounds in the two nonverbal conditions, and between 'living' and 'non-living' objects in both verbal conditions (pictures and words). All 4 runs were presented in a single session.

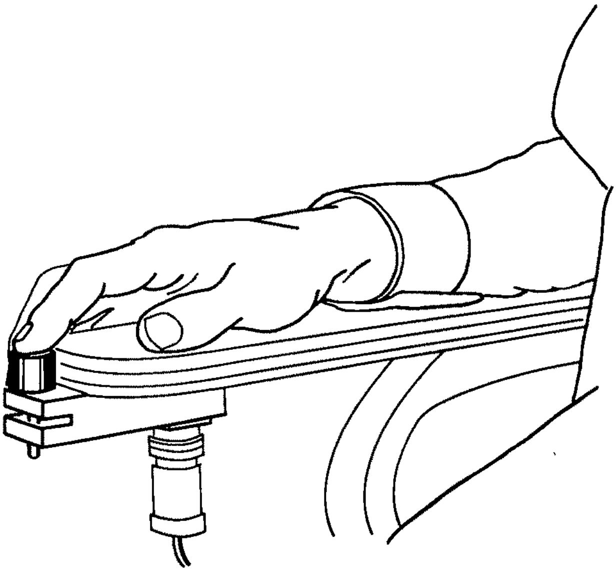

FIG. 1 Position of right index finger on the button during the experimental session. The response is isometric, i.e. the button is stationary and no overt movement can be felt during the response performance. Throughout each test session the subject was required to keep both index fingers resting on the corresponding buttons.

During the test session the subject was seated in a chair with a button and pressure transducer fitted to each armrest (fig. 1). Throughout the tests the subject was instructed to hold the index finger of each hand on the corresponding button. Absence of a blinking light indicator for each hand provided feedback that the baseline pressure was maintained. The task was to respond to each stimulus by pressing the designated button 'as quickly as you can, and as correctly as you can'. A second light indicator for each hand provided continuous feedback when the criterion force was reached by remaining lit during the time for which the criterion was exceeded. The criterion was set at 294.3 centiNewtons (cN) of force (corresponding to 300 g of mass). Force data were always analysed in the log transformed form, so the criterion of 294.3 cN becomes 2.469 log cN. The reaction time response was continuously recorded as the amount of force exerted by the subject's index fingers on the pressure transducers during baseline, response execution, and return to baseline.

There were 72 stimuli in each of the nonverbal conditions, 120 pictures, and 96 word stimuli. Of the 13 demented subjects, 8 were able to complete all 4 stimulus conditions with a full complement of trials. The remaining 5 had abbreviated test runs, terminated after 36 to 40 responses due to signs of restlessness. Two of these subjects were not tested at all with line stimuli, and one was not tested with words. For this reason, the statistical analysis (*below*) consists of comparisons between 10 senile and 34 control subjects.

Dependent Variables

Ten measures were extracted from the force records for every registered response. The first step in the analysis of each response was to locate the six reference points illustrated in fig. 2. Point A indicates the moment of stimulus onset. C and D mark the points where response force crosses the criterion of 294.3 cN on the way up and on the way down, respectively. Point B, which divides the premotor and motor intervals, was determined statistically. The first 16 data points (totalling 256 ms) following stimulus onset were used to calculate a baseline variance. Then, beginning with the seventeenth data point, the variance of 7 consecutive 16 ms intervals was computed and compared to the baseline variance in an F-ratio with df of 15 and 6. If the probability of that F-ratio was greater than 0.01, the 7-point window was shifted one point to the right and a new variance and F-ratio was computed—and so on until a significant F-ratio ($P < 0.01$) was obtained. The midpoint of that window was marked as point B. *Premotor time*, then, was computed as the interval between points A and B, and the *baseline* force as the mean force applied during that interval.

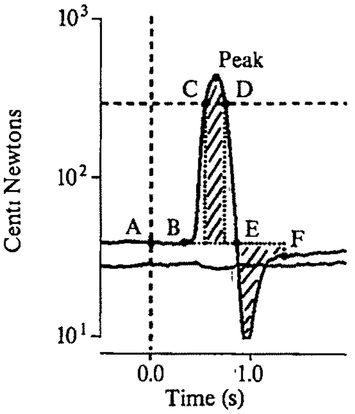

FIG. 2. Hard copy of a button-press response, showing the six reference points used to define ten dependent variables. The vertical dashed line indicates onset of stimulus. The horizontal dashed line indicates the criterion force of 294.3 cN (2.469 log cN). The two analog tracings represent the force record from the responding hand (labelled curve), and from the nonresponding hand, respectively. Force is plotted against a logarithmic scale, which enables the observation of small variations at low force levels near the baseline and provides substantial compression at high force levels above the response criterion. The ten dependent variables are explained in the text.

Motor time was defined as the interval from B to C. *Response duration* was taken as the interval between C and D, and the *peak force* was taken as the highest force recorded during that interval. *Response time integral of force* is the sum of all forces recorded between C and D (crosshatched). Point E marks the point where response force first crosses the baseline level as the button is released. The D–E interval was taken as the *release time*. Finally, point F was arbitrarily set at 512 ms following the release point E. The total of absolute differences between the baseline force and the recorded force during this interval was taken as the measure of *undershoot* (crosshatched). Similarly, the force changes of the nonresponding hand (*contralateral overflow*) was calculated for the interval between points B and F. In this manner, the response time integral of force, undershoot and contralateral overflow all represent a time integral of force for the specified interval and are expressed in force-over-time units.

The last index of response generation, *coefficient p*, was calculated by exponential fitting of the 640 ms long interval preceding point C. This was done in order to obtain an index of sharpness of the force rise at the leading edge of the response (for detailed description of the calculation, *see* Vrtunski and Mack, 1982). For very slowly generated responses, coefficient p is typically below 5, for slow responses between 5 and 8, for normal responses between 8 and 12, and for responses with very steep force rise, the coefficient p may well exceed 12.

Computer programs were developed to derive the described ten dependent variables from each recorded button-press response. The scores assigned to each subject and each stimulus condition are the arithmetic means of each variable.

Data Analysis

Two types of data analysis were performed. Qualitative analysis consisted of visual examination of the hard-copy graphs of individual responses with the objective of discerning distinct features which might characterize the two subject groups. Quantitative evaluation was performed with the analysis of variance of the BMDP '81 library (Dixon, 1981).

RESULTS

Analysis of response omission and accuracy rates shows that the choice reaction time task was a difficult one for the Alzheimer subjects. They failed to respond to 5.66 per cent of the stimuli in the easiest (auditory-nonverbal condition), and to 22.0 per cent of the more difficult (auditory-verbal) trials. Of the responses registered, the correct choice was made 93.1 and 82.4 per cent of the time, respectively. In control subjects no omission errors were recorded, and the correct choice was made 99 per cent of the time in all stimulus conditions except the auditory-verbal, where it was 91.1 per cent. Normal controls, following an erroneous choice, often corrected themselves by immediately responding with the other hand. These bimanual responses were deleted from the analysis. SDAT subjects, on the other hand, showed no such tendency. In the auditory-verbal condition with normal subjects, erroneous choices (commission errors) were made more frequently due to past learning, we feel, than due to failure of comprehension. Words like 'moon', 'soil', and 'water' were frequently classified as 'living'.

Qualitative Analysis

Visual inspection of individual button-press responses most dramatically reveals the behavioural differences between normal elderly and Alzheimer subjects. For normals, the behavioural sequence consists mainly of two clearly distinguishable parts: a quiescent premotor segment, followed by a quick burst of force resulting in button depression and subsequent release (fig. 3A). The demented subjects, on the other hand, showed a great deal of apparent indecision prior to response execution. In many cases, the force increase up to the criterion level is fragmented, and only the last segment may contain a clearly distinguishable fast force rise (fig. 3B). Such slow force rise is often followed by a long 'hold', that is, an interval of constant force, which is presumably needed for deciding to release the button (fig. 3C).

Another major contributor to long motor times is what we call a preresponse drop, seen in fig. 3D as a major decrease in the baseline force just before onset of the response proper. Although such drops are also occasionally observed in the responses of normal subjects, they are usually shorter and relatively shallow. For demented subjects, however, the preresponse drop can be very large, and it may represent either a termination of the baseline maintenance portion of the task before 'embarking' on the next portion (of response generation), or it may represent an inverted form of the slow force rise. These force changes (up or down) are independent of forces applied by the nonresponding hand, which implies that the

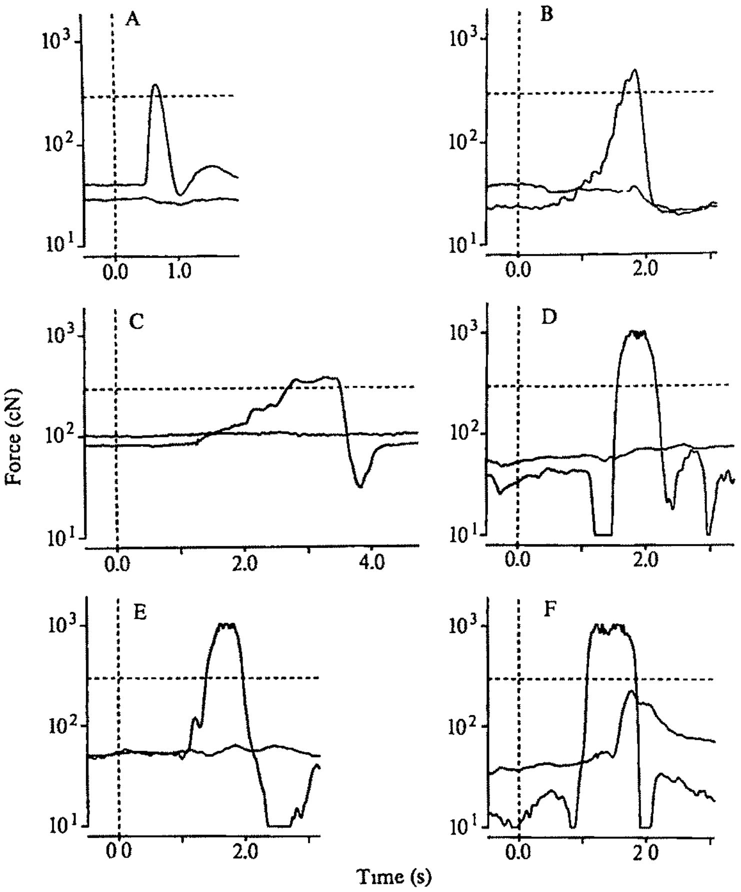

FIG. 3. Comparison between a control (A), and several SDAT subjects' responses (B–E) Visual inspection of these responses illustrates several deviations from normal performance. In B there is a long motor time resulting from slow force rise and in C, a long response duration resulting from slow movement reversal. The remaining three responses, recorded from one subject under the same stimulus condition (sounds), illustrate a large preresponse drop (D, F), a large undershoot (E), and a large contralateral overflow (F). Responses of this subject under all stimulus conditions also showed prominent hyperdynamic features, i.e. peak forces more than three times greater than the criterion required. Although the visual inspection of responses provides a direct route to appreciation of differences between control and SDAT subjects, quantitative measurements of each response provide the means for data reduction. Thus the response illustrating a control subject's performance originated from a baseline of 1.6101 log cN, was preceded by a premotor time 432 ms long, and included a motor time 160 ms long. Coefficient p calcuated from a 640 ms segment preceding point C (*see* fig. 2) was 8.57, i.e., the best-fitting curve describing the force rise is y = aexp $(bx^{8.57})$. The response itself (the segment exceeding the criterion) was 144 ms long, and contained a force expenditure as measured by time integral of force of 0.1208 log cN-s. The peak force was 2.586 log cN. The response was followed by an undershoot of 0.0868 log cN-s, and was accompanied by a contralateral overflow in the nonresponding hand of 0.0318 log cN-s. For the purpose of comparison, some values from the demented subject's responses are as follows. The slow rise response (B) had a motor time of 1008 ms (with the coefficient p of 2.09) The one with preresponse drop (D) had a motor time of 432 ms. The response duration of the long 'hold' response (C) was 832 ms, and the force expenditure was 0.519 log cN-s. The undershoot illustrated in E was 0.529 log cN-s, and the contralateral overflow in F was 0.525 log cN-s. The maximum peak force observed in the last three responses was 3.011 log cN. This represents an erroneous reading because it was also the ceiling of the instrument's capability Nevertheless, the abnormality of these responses, both in terms of baseline maintenance and the force distribution, is easily recognized.

choice of hand (the cognitive processing of stimulus information and deciding which hand is to perform the response) is completed before the beginning of the motor interval.

In addition to clarifying the nature of long motor times and long response durations, visual inspection of button-press responses is helpful in observing the increase in undershoot (fig. 3E) and contralateral overflow (fig. 3F) in demented subjects. These are related to release time and baseline maintenance, respectively (*see* Discussion).

There was a great deal of individual difference in performance among the SDAT subjects. For 6 subjects, differences in motor performance across the various stimulus conditions were clearly distinguishable. Comparisons of their 'best' and 'poorest' type of responses are illustrated in fig. 4. Only for one out of those 6 subjects did we find a steady improvement across successive test sessions (fig. 4A, B).

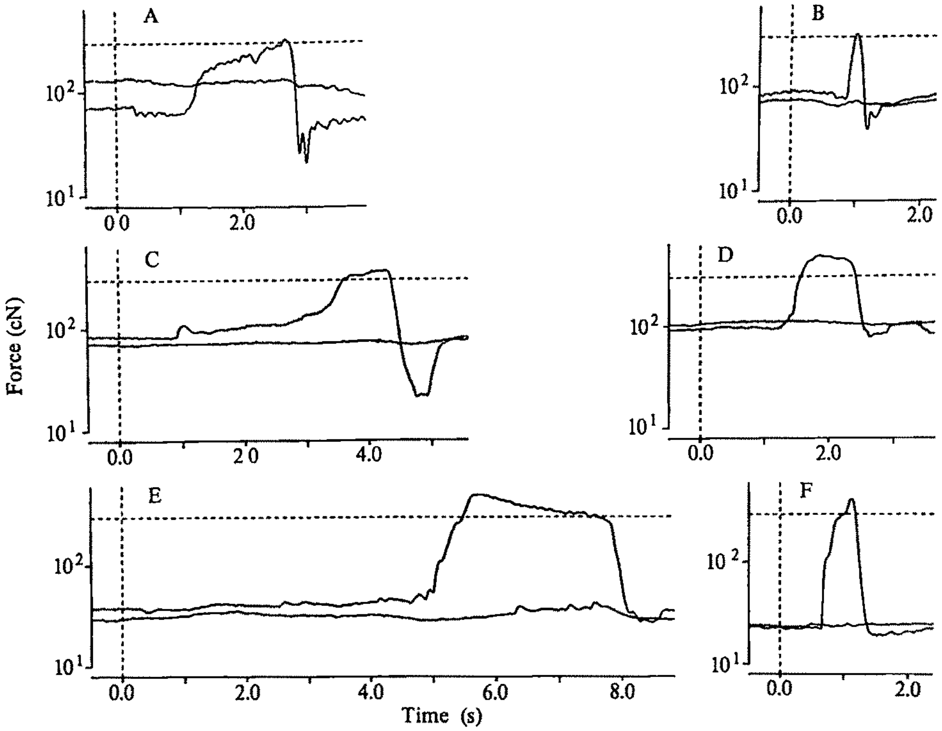

FIG. 4. Comparison between the 'poorest' and the 'best' responses in 3 SDAT subjects The first pair of responses was generated by a 62-year-old man for lines (A) and sounds (B), respectively. This subject showed considerable improvement with practice (the session with lines was administered first, the session with sounds last in sequence). In fact, his performance with sounds was indistinguishable from that of control subjects. The second pair of responses came from a 59-year-old man, with pictures (C) last in the testing sequence, and sounds (D) third in the sequence. Although long responses were observed in both instances (the mean response durations were 771 and 1083 ms, respectively), the difference in motor times was much greater (1064 and 377 ms, respectively). The third subject illustrated was a 72-year-old woman. Her 'poorest' performance was with words (E), administered last, while the 'best' performance was with pictures (F), administered first in the testing sequence

Since other subjects did not show any such practice effect, specific task requirements were probably responsible (fig. 4C–F).

Finally, we did learn about an aspect of CRT performance in SDAT subjects from those 3 who were dropped from the statistical analysis because of failure to complete all trials. All 3 were very impaired on the button-press task. One of them, for instance, was not able to maintain baseline contact of index fingers with the button. Instead, she chose to hold her hands several inches above, and the generated response consisted simply in a sharp drop and withdrawal of the lower arm. No amount of coaching helped her past the initial few responses; the subject would immediately return to the described manner of responding. This pattern of performance supports our earlier interpretation that the baseline maintenance represents a separate behavioural task, which in some instances seems to be incompatible with the remainder of the task. With another subject who also showed great difficulty in the CRT task, we attempted a unimanual choice procedure. Instead of making a choice to respond with left or right hand, the subject was asked to use only one hand, and to respond only to one class of stimuli and not to another. Under these conditions, the subject was able to perform with all stimulus conditions, and it was our impression that the task was 'easier'. In other words, just maintenance of the bimanual baseline and inhibiting one hand while the other is used for response may represent a sufficient load in advanced senility to preclude a more common CRT performance pattern. Indeed, a careful systematic analysis may reveal that each component of the task has a specific 'weight' in psychomotor performance of this type.

On the basis of these observations concerning the response analogs, we conclude that the isometric button-press response in SDAT subjects lacks the psychomotor organization that is characteristic of a preprogrammed output, that is, it represents a disintegrated motor event. Although the quantitative indicators of the RT performance will help us in further elucidation of the nature and extent of disintegration, visual inspection of individual responses provides an immediate route to observing the gross differences between subjects and may prove to be a useful tool in clinical work.

Quantitative Analysis

The arithmetic means and standard deviations for ten variables under four stimulus conditions are presented in Table 1.

Although the number of demented subjects is small and therefore the subject-to-variable ratio is low, statistical evaluation of data was performed with multivariate analysis of variance. Its summary is presented in Table 2. Results indicate large differences between the two groups. Of the ten measures, only baseline, response peak force, and coefficient p did not show significance (though the last two measures were close to the critical limit, 0.0570 and 0.0756, respectively). On the basis of univariate F values for the group factor, the largest difference observed was in motor time, followed by premotor time, contralateral overflow, response duration, and so on. An unexpected observation was that concerning release time, namely, while

TABLE 1 MEANS AND STANDARD DEVIATIONS FOR 10 DEPENDENT VARIABLES AND 4 STIMULUS CONDITIONS IN CONTROL ELDERLY (n = 34) AND SDAT (n = 10) SUBJECTS

	Lines				*Pictures*			
	Controls		*SDAT*		*Controls*		*SDAT*	
Dependent variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1. Baseline (log cN)	1.68	0.239	1.60	0.234	1.64	0.187	1.59	0.227
2. Premotor time (ms)	462	133.7	788	230.9	636	130.1	1091	487.5
3. Motor time (ms)	187	52.2	665	493.0	226	74.4	849	541.8
4. Response duration (ms)	256	184.7	485	348.3	245	190.5	373	245.7
5. Release time (ms)	160	55.8	124	32.5	166	39.4	114	42.5
6 Response peak force (log cN)	2.71	0.132	2.79	0.144	2.69	0.125	2.77	0.165
7. Time integral of force (log cN-s)	0.255	0.240	0.516	0.423	0.258	0.240	0.384	0.262
8. Undershoot (log cN-s)	0.174	0.118	0.278	0.148	0.209	0.118	0.283	0.163
9. Contralateral overflow (log cN-s)	0.063	0.047	0.123	0.088	0.065	0.040	0.147	0.103
10. Coefficient p	13.18	9.45	8.25	4.38	10.26	3.68	7.30	3.88

	Sounds				*Words*			
	Controls		*SDAT*		*Controls*		*SDAT*	
Dependent variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1. Baseline (log cN)	1.66	0.200	1.58	0.247	1.65	0.237	1.61	0.194
2. Premotor time (ms)	802	109.8	1037	260.2	1135	164.6	1705	557.2
3. Motor time (ms)	209	50.2	602	396.6	325	116.4	1348	866.9
4. Response duration (ms)	250	165.2	506	367.6	303	274.9	825	744.7
5. Release time (ms)	168	47.4	126	47.4	180	53.8	108	46.6
6. Response peak force (log cN)	2.70	0.121	2.80	0.208	2.70	0.122	2.81	0.231
7. Time integral of force (log cN-s)	0.250	0.202	0.546	0.358	0.311	0.343	0.911	0.894
8. Undershoot (log cN-s)	0.158	0.095	0.227	0.107	0.152	0.102	0.256	0.157
9. Contralateral overflow (log cN-s)	0.053	0.029	0.133	0.066	0.074	0.074	0.294	0.348
10. Coefficient p	10.90	3.74	9.72	5.69	9.98	4.66	7.13	4.46

other response segments show significantly longer durations in the demented group, the release time was shorter than in controls. We believe this to have an important bearing on the manner in which the button-press response is being organized in those two groups.

While the demented subjects were expected to differ from the normal controls on several measures of response generation, the effects of stimulus condition on variables other than premotor time were not fully anticipated. The stimulus effect on premotor times is due in part to the difference between temporal extension of auditory stimuli (average length 768 ms) in the visual-auditory comparison, and in part due to the difference between cognitive loads (within each sensory modality) for the nonverbal-verbal comparison. Indeed, across the four stimulus conditions, premotor time showed the most pronounced changes. This explanation, however, does not extend to other dependent variables. The traditional assumption is that cognitive processing is terminated before onset of response. Once the response is

TABLE 2. SUMMARY OF MULTIVARIATE ANALYSIS OF VARIANCE WITH F-RATIOS AND EXACT PROBABILITIES FOR EACH SIGNIFICANT ($P < 0.05$) SOURCE OF VARIATION

	Group factor		*Stimulus factor*		*Group × stimulus interaction*	
Source	*F*	*P*	*F*	*P*	*F*	*P*
Multivariate ratios	10.26	0.0000	33.29	0.0000	8.42	0.0001
Probability for df of		10,33		30,13		30,13
Univariate ratios						
Baseline	0.80	—	0.72	—	0.62	—
Premotor time	52.46	0.0000	177.16	0.0000	10.59	0.0000
Motor time	73.86	0.0000	11.55	0.0000	13.96	0.0000
Response duration	12.18	0.0011	2.83	—	4.48	0.0084
Release time	11.43	0.0016	1.27	—	1.91	—
Response peak	3.83	—	0.97	—	0.76	—
Time integral of force	10.11	0.0028	2.54	—	5.81	0.0021
Undershoot	6.11	0.0176	4.32	0.0099	0.42	—
Contralateral overflow	21.71	0.0000	2.68	—	4.03	0.0135
Coefficient p	3.32	—	5.01	0.0048	1.15	—
Probability for df of		1,42		3,40		3,40

'triggered', it is expected to be the same and independent of stimulus type. Yet a significant stimulus factor in motor time, coefficient p and undershoot, clearly points toward an alternative interpretation (response duration, contralateral overflow and time integral of force, also came close to critical limits, with probabilities of 0.0507, 0.0601, and 0.0703, respectively).

To gain a clearer perspective as to how to interpret the stimulus effects on response components occurring after the premotor segment, the F-test (one-way repeated measures ANOVA) was used for each dependent variable separately using only data from the control group. Of the ten, seven variables were statistically significant across the 4 stimulus conditions (df 3,99 in each case): premotor time ($F = 341.53$, $P = 0.0000$), motor time ($F = 26.50$, $P = 0.0000$), response duration ($F = 2.76$, $P = 0.0464$), release time ($F = 3.09$, $P = 0.0305$), time integral of force ($F = 2.92$, $P = 0.0380$), undershoot ($F = 4.68$, $P = 0.0042$), and coefficient p ($F = 4.20$, $P = 0.0077$). The Newman-Keuls test of these differences revealed that in three variables (response duration, release time, and time integral of force) their source is primarily in the three contrasts involving words, with undershoot—three contrasts involving pictures, and with coefficient p—with lines. With motor time, only the difference between pictures and sounds was not significant, and with premotor time, all six contrasts were highly significant.

In view of the small number of SDAT subjects, and larger variability between them, similar statistical tests are certainly less reliable. Nevertheless, the repeated measures ANOVA on SDAT subjects alone indicated significant differences between premotor times ($F = 10.89$, $P = 0.0001$), and motor times ($F = 4.84$,

$P = 0.0080$) for the four stimulus conditions (with response duration and time integral of force approaching the critical limit, that is, probabilities of 0.0842 and 0.0796, respectively).

As a final check for the effect of varying stimulus loads on some of the response measures, an inspection of individual premotor and motor times, response durations and release times was made for each control subject individually. Of the 34 subjects with two nonverbal-verbal comparisons each (visual and auditory), the verbal tasks generated longer premotor times in 98.5 per cent of cases, longer motor times in 79.4 per cent of cases, longer response durations in 60.3 per cent of cases, and longer release times in 50.0 per cent of cases. (A similar check on data from senile subjects yielded 85, 90, 45 and 45 per cent, respectively.) Hence we conclude, first, that the task demand effects can be traced to an individual subject's performance, and secondly, that in four consecutive response segments the effect of cognitive load is gradually diminishing (i.e., the 50 per cent value is interpreted as an absence of effect). The second conclusion has a very important place in our interpretation of the button-press response dynamics (*see* Discussion).

Returning to the multivariate analysis of variance and the significant group × stimulus interaction terms, which were observed in five variables (Table 2), inspection of plotted means (fig. 5) indicates that their source is either in lack of parallel changes in two groups due to different stimulus conditions (such as in premotor time and time integral of force), or due to disproportionately greater differences in senile *vs* control groups (motor time, response duration and contralateral overflow). Due to the large differences between the two groups overall, and the variability within the SDAT group's performance, an interpretation of these interactions should be made with caution. Even so, it is tempting to speculate that the source of significant interactions is the difference in the task handling capabilities of the two groups, or more specifically, that the constraints under which Alzheimer subjects operate are qualitatively different from that of normal ones. The time integral of force in SDAT group with words, for instance, is more than twice that for pictures. Even lines and sounds are accompanied by greater forces than pictures. Such a large disparity between two verbal tasks was not observed in any other performance measure in either of the two groups.

DISCUSSION

In this study, the isometric button-press response of normal elderly and demented subjects was analysed and compared using a procedure based on the notion that 'force can be looked upon as the body's basic output quantity' (Bates, 1947). In other words, the traditional approach of studying reaction time alone was replaced by the study of actual behaviour during that time. This was accomplished by measurement of forces. The results clearly demonstrate that even such an apparently 'simple' motor act as pressing a button in fact contains several distinct components reflecting various aspects of psychomotor organization.

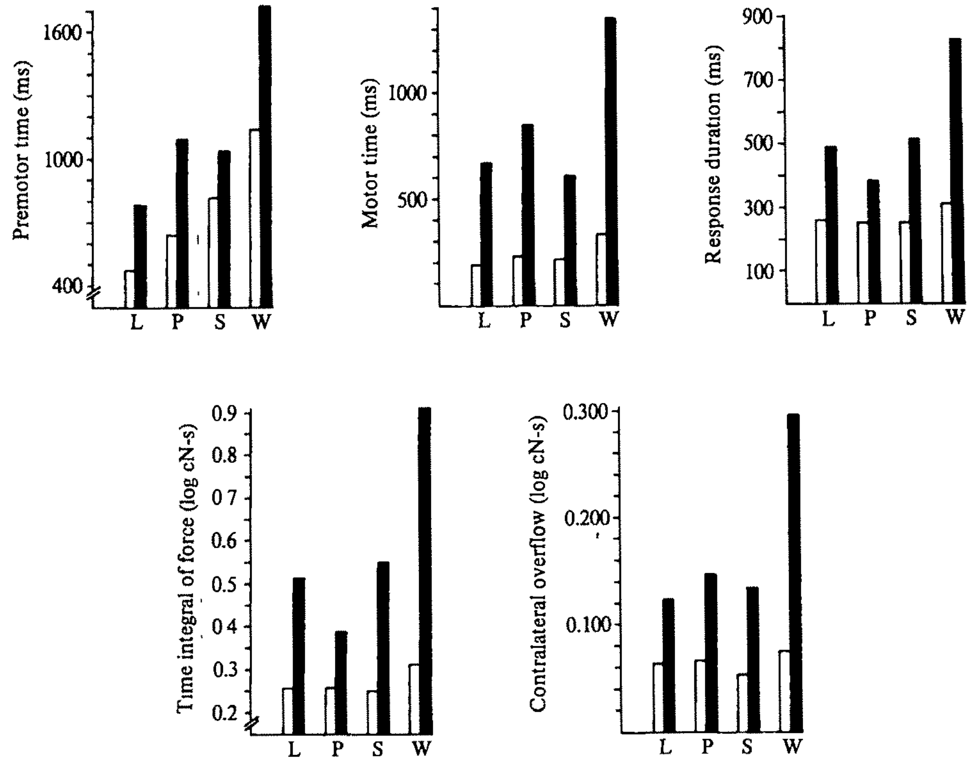

FIG 5. Graphic representation of five variables where the significant group × stimulus condition interaction was observed. L, P, S and W indicate lines, pictures, sounds and words, respectively. □ = controls. ■ = SDAT.

There are two major issues which require substantial elaboration. One is related to the observation that differences in task requirements affect the qualitative aspects of the response itself, and the other is related to relatively large differences between normal and senile subjects that we studied. We will attempt to show that these two issues are not independent, but to suggest that they are intimately related to each other. In order to arrive at this interpretation we have first to examine the response itself.

Response Variables

Quantitative analysis of the data was based on an admittedly artificial scheme, referenced to the preresponse baseline and an arbitrary response criterion force of 300 g. A total of ten numerical indices of performance were computed, nine of which represent actual physical measurements. The tenth, coefficient p, represents a mathematical function derived by a curve-fitting procedure. An obvious question is whether so many indices are needed to describe a button-press response. It is our belief that multiple indicators are required at present, both because of the complexity of the motor performance and of a lack of information describing it. We observed, for instance, that response duration, time integral of force and peak force are highly intercorrelated variables (Vrtunski and Mack, 1982). Yet it would be premature to abolish two of those and use only one, as long as we do not know the exact relationship between the three variables.

The most direct approach to the button-press response itself is in the direct examination of the four principal components which were defined by their durations. A 'normal' response is seen to originate from a steady well-controlled baseline (as reflected in premotor time), followed by a smooth force rise (motor time), reversal of movement direction (response duration), and final return to a steady baseline (partly reflected in release time). Of these four components, only premotor time was traditionally subdivided, namely into sensory (input), cognitive (encoding), and decision making (output programming) stages (*see* Botwinick, 1973). Allocation of segmental time within the premotor time, unfortunately, is beyond the reach of the present behavioural techniques. Due to our observations which indicate that virtually every dependent variable is affected by the cognitive load of the given task, it seems reasonable to assume that every subcomponent of the premotor time alone is also subject to cognitive load effect. If in a more difficult task we register a longer motor time, for instance, it is very likely that the output programming within premotor time was also longer.

Motor time in the 'normal' response represents a complex chain of events. Within the interval as we measured it, at least three subcomponents can be recognized, response initiation, a fast force rise, and an onset of slowing which precedes reversal in force direction. The preresponse drop as described in demented subjects (fig. 3D, F) is the most prominent marker, suggesting that transition between quiescent baseline and fast force rise is not continuous. Similar events, although on a smaller scale, were observed in normal subjects. That the fast force rise may represent a separate component, we base on the very fact that the movement velocity during this segment is highest, and by inference, the result of activity of specific neuronal elements. On hard-copy records with 'zoomed' time scale, it could be readily observed that the point of maximum velocity is located 50 to 100 ms before response criterion, 100 to 150 ms before the peak. Similar observations of velocity changes can be observed on records from studies of monkey arm movement (Brooks, Cooke and Thomas, 1973). We believe that the slowing subsequent to the point of maximum velocity may not represent a simple fading out of the fast force rise, but rather a third subcomponent, a preparation for the forthcoming reversal in movement direction.

The movement reversal as described by response duration appears as a unitary event, primarily in control subjects. With word stimuli, however, it was significantly longer than in the other three conditions and it is questionable whether it is due simply to slower evolution of the two neighbouring components (motor and release times) or whether it represents two separate elements of flexion-to-extension change. Our results clearly indicate that in SDAT subjects this transition can be interrupted (fig. 4).

Finally, release time also seems to represent a composite event. Having in mind that it was differentially affected by stimulus conditions in control subjects and that group comparison showed SDAT subjects to have shorter release times, our interpretation is that there are at least two subcomponents in this response segment. One is an active 'pull' away, which results in finger extension, followed immediately by a 'brake' to recover the baseline without excessive undershoot (complete release of the button was signalled by a blinking red light). Utilization of braking in voluntary movements is well established. It is part of programmed motor output whenever the agonist force exceeds the viscoelastic forces alone (Lestienne, 1979). Therefore, our results suggest that, first, the agonist-antagonist synchrony, that is, braking, may be modified by task demands, and secondly, that senile subjects are not using this synchrony appropriately, or alternatively, use of the braking may represent an excessive task demand altogether. Significantly shorter release time and greater undershoot in the SDAT group strongly suggests the second possibility.

In summary, except for premotor time, the three segments of the button-press response that we measured provide an objective basis for investigating truly microbehavioural subcomponents of motor output and their relationship to cognitive load. Premotor time, which is in many ways the most interesting aspect for behavioural scientists because it constitutes the basis of sensory-cognitive-motor interrelationships, can only be considered by indirect inference. What remains to be examined is the wider framework of psychomotor organization and cognitive aspects of the response.

Psychomotor Organization

The comparison between normal elderly and demented subjects clearly brings out a characteristic of the response which could be well described by the term psychomotor organization. Our interpretation of responses observed in the demented group, therefore, could best be described as an absence of this organization, providing evidence of psychomotor disintegration. It may be questioned whether high precision measurements are needed to come to a seemingly obvious conclusion. Our assumption is that psychomotor organization is not a present-absent type of characteristic of behavioural output, but rather that between 'normal' and 'disintegrated' performance there are many shades of deterioration which can be detected only by high resolution tools. This belief is well supported by a follow-up on several demented subjects from this study, who upon retesting after one year showed a significant decline in reaction time performance (Vrtunski *et al.*, 1982).

Concerning the organization of motor output, the theoretically most developed framework is found in Bernstein's well known monograph (1967). His theory of motor coordination is important for several reasons: it suggests the presence of microbehavioural components of the motor output as finite behavioural units, and it postulates their organization as a unifying principle. Furthermore, economy of effort, or psychomotor efficiency, is considered to be the main rule governing this organization.

Bernstein and his collaborators used the kymocyclographic analysis of movement, while the interpretation is largely cybernetic. In describing closed-loop control, Bernstein uses the well known concepts of input, reference and resulting error signal. His postulates are referred to the level of the 'microstructure' of the movement (pp. 114–142). Thus, the 'microintervals', presumably the elementary units of time in movement performance, are believed to be 70 to 120 ms long, and the operation of the loop is largely described as if driven by an 8 to 14 Hz clock. In order for the motor programme to flow continuously, two additional elements have to be taken into account, namely, a memory component and an anticipated error signal. In Bernstein's words, 'the current micro-regulation of movement shuttles constantly between the present moment t and the limits of the interval from $t-\Delta t$ ('fresh traces') to $t+\Delta t$' (the anticipatory reference signal). On a more complex level, Bernstein proposed that 'the co-ordination of a movement is the process of mastering redundant degrees of freedom of the moving organ, in other words its conversion to a controllable system'. The elimination of redundant degrees of freedom, however, occurs after the first few attempts in performance of the given movement. On subsequent attempts, a more 'economic method of overcoming the redundancy through the organization of the process as a whole' is used.

The most direct evidence for the presence of the microbehavioural components comes from a series of studies by Brooks and his collaborators on cerebellar control of voluntary movement in cebus monkeys. Two major types of movements were distinguished, continuous and discontinuous. The first was characterized by a relatively smooth and ballistic-like force expenditure, while the second consisted of a number of small steps only gradually approaching the intended goal (Brooks, Cooke and Thomas, 1973). Both types of movements were seen in all animals tested, yet the animals which had a longer distance to traverse generated predominantly discontinuous movements, while the animal with shorter distances generated predominantly continuous movements (Brooks, Kozlovskaya *et al.*, 1973, p. 982). Whether shorter and longer distances of the task could be equated with 'easier' and 'harder' in human terms, is not known. These authors demonstrated that the two types of movement can readily be analysed in terms of frequency content (Brooks, Cooke and Thomas, 1973).

Cognitive Aspects

In a wider theoretical framework, we assume that there are at least two constraints operating in the microbehavioural experiment: (1) internal, that is, the subject's capacity for psychomotor organization, which is a function of CNS integrity and/or maturational stage, and (2) external, that is, task difficulty. Both should be thought of as continuous, mutually independent variables. Yet, with appropriate control of both, we should be able to obtain a considerably deeper understanding as to how the information is being processed or what is defective in the performance of a given subject. This is expected because the relationship between microbehavioural components is not assumed to be 'hard-wired' or stable. The button-press response may appear fixed and 'reflex-like' only under the least demanding conditions. Once the external constraint, for instance, is imposed in some finite amount, the 'tightness-of-links' between components is attenuated. We can register increases not only in premotor time, but also in motor time, response duration, and so on. In other words, we are seeing a very specific trade-off relationship between what the system can and what it is requested to perform.

Varying the internal constraints is not readily amenable to experimental control. Our study of normal and demented subjects in this respect may be seen as a comparison of two widely separated groups. Yet to observe the degree to which the response can become impaired is an obvious step toward recognizing the range of changes which can be expected in this psychomotor performance. Obviously, the study of subjects with less disintegrated output should provide us with a more detailed picture about the stages through which psychomotor decline develops.

Although the external constraints are under experimental control, a number of assumptions, yet to be examined, have to be made. To account for the observations presented here, we assume that the cognitive demand of the task can be expressed in terms of the number of 'search', 'identify', and 'compare' operations during the encoding and decision-making stages of the premotor time. This assumption is an implicit part of any discussion of cognitive functions. The mere number of these operations, we believe, is what contains the key as to how well the subsequent psychomotor organization will be performed, that is, the greater the number of operations needed, the lesser degree of organization will be accomplished in the forthcoming response. The observation that the cognitive load effect is gradually diminishing from premotor to motor, to reversal and to release times points to the premotor time as the prime locus of this 'disorganizing' effect of cognitive operations.

Why psychomotor organization would be inversely proportional to cognitive load is far from obvious. In order to account for simultaneous performance of more than one task, namely, interference, overflow, etc., in a competing task, Kinsbourne and Hicks (1978) postulated a concept of functional cerebral space which, similar to Kahneman's (1973) model of attention, has a finite capacity. Furthermore, each of the competing tasks is controlled by specific neuronal elements. Consequently, the amount of interference observed depends on the 'functional distance' between the control centres. In our experimental procedure, during the premotor or decision-making time, the subject was simultaneously required to maintain a steady baseline. However, interference with baseline maintenance by cognitive processing was not apparent, in that levels of baseline did not vary appreciably between stimulus conditions. Baseline maintenance appears to be a 'steady-state' type of variable; the subject adopts a certain level and maintains it throughout the session, and from one stimulus condition to another. If the interference model could be used, we consider that it would have to reflect cognitive operations and their effects throughout the subsequent stages of the programming and execution of the response. Experiments with systematic control of baseline and response criterion force requirements, for instance, would be most helpful in the further elucidation of the nature of this interference.

In a recent review, while describing the approach of cognitive scientists, Pachella stated 'reaction time is often chosen as a dependent variable by default: there simply isn't much else that can be measured' (1974). This attitude reflects, in our opinion, an implicit and deeply held assumption that there is no aspect of overt behaviour, except for the occurrence of the response itself, which can provide the relevant insight about information processing in cognitive functions. In operational terms, it is a reduction of behaviour to latencies of binary or 'all-or-nothing' events.

The approach taken and results obtained in this study provide a different perspective. First, we demonstrated that a button-press response can be meaningfully analysed in terms of its components and that such analysis yields a more comprehensive understanding of motor output. Secondly, while it is true that behaviourally, premotor time (the presumed cognitive stage) remains unbroken, the observation that subsequent motor output can be modified by the content of what is being processed represents an important addition to the study of cognitive-motor relationships, both in theoretical and applied areas.

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PRIMARY POSITION UPBEATING NYSTAGMUS

A VARIETY OF CENTRAL POSITIONAL NYSTAGMUS

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SUMMARY

We report a collaborative study of 11 patients with upbeat nystagmus in the primary position of gaze. In most cases the nystagmus behaved in accordance with Alexander's Law; in 3 patients convergence enhanced the nystagmus. Lateral gaze was without effect in 7 instances. Static tilt to prone and supine positions altered the characteristics of the nystagmus in 7 patients. The effects were variable and, in one case, there was reversal of the direction of the nystagmus to downbeating. There was pathological or radiological confirmation of lesions in the pontomedullary junction (2 cases) and the ponto-mesencephalic junction (2 cases). The findings support previous reports that primary position upbeat nystagmus occurs predominately with intra-axial brainstem lesions. There is one report of its occurrence with an intrinsic cerebellar lesion. Modification of the amplitude of upbeat nystagmus by tilt of the head with respect to gravity in the majority of patients implies an otolith-related component in the genesis of the nystagmus.

INTRODUCTION

Upbeating nystagmus in the primary position of gaze is a neurological sign which is rarely identified. The nystagmus is characterized by a downwards drift of the eyes when the patient attempts to maintain the primary position of gaze. The drift is interrupted by saccadic movements which correct eye position back towards centre and give rise to the upward beating appearance of the nystagmus. The amplitude of the nystagmus, as we shall describe, is frequently modulated by tilting the patient with respect to the direction of gravity and consequently, in certain positions, may be so small that detection is difficult unless the patient is examined in a variety of postures.

Despite a considerable volume of literature on nystagmus in the vertical plane, the specific direction has often been ignored and the few previous examples of upbeat nystagmus reported have been single case studies. These have lead to generalizations about the behavioural characteristics and origins of the nystagmus which are unwarranted and misleading. This paper describes upbeat nystagmus in 11 patients and the findings have enabled us to demonstrate important aspects of its behaviour. Of particular interest is the influence of otolith stimulation, which provides insight into the pathophysiology of nystagmus in the vertical plane. In addition, the autopsy and radiological findings in 4 of our patients who had discrete lesions have enabled us to define the sites of the lesions responsible for upbeat nystagmus more accurately.

METHODS

A full neurological assessment was made of each patient; in addition the following tests of oculomotor and vestibular function were performed. Eye movements were recorded using d.c.-coupled electro-oculography. Detailed observations were made which included the velocity and range of eye movements and associated nystagmus in the vertical and horizontal planes in both light and darkness, responses to pursuit and optokinetic stimulation in vertical (using a projection screen) and horizontal (whole field rotating drum) planes, the effects of convergence, responses to rotatory vestibular stimuli about vertical and horizontal axes and responses to static tilt with respect to gravity. Tilting was performed using a triaxial gimbal which was large enough to take an adult secured in either a seated or supine position. The head, trunk and limbs were fixed with harnesses so that no differential movements of the cervical and thoracic segments of the vertebral column or the head were induced by the tilting movement. Tilt was transduced by a precision angular accelerometer (Schaevitz AMP-50) and the rate of tilt was variable up to an angular velocity of 45 deg/s. Angle of tilt with respect to gravity was transduced using a precision piezo-resistive linear accelerometer (Endevco 7265-20).

PATIENTS AND OBSERVATIONS

A summary of the electro-oculographic findings is given in Table 1.

TABLE 1 ELECTRO-OCULOGRAPHIC CHARACTERISTICS OF UPBEAT NYSTAGMUS

Case No	*Sex, age (yrs)*	*Diagnosis*	*Alexander's Law*	*Convergence*	*Darkness*	*Lateral gaze*	*Static tilt*
1	M, 42	Ependymoma fourth ventricle (postoperative)	—	Enhanced	Enhanced	No effect	Supine—increased Prone—abolished/ inverted to downbeat nystagmus
2	F, 34	Multiple sclerosis	+ with exp waveform	No effect	Enhanced	Enhanced	Not done
3	M, 60	Brainstem infarct	+	Abolished	Enhanced	No effect	Supine and prone—abolished
4	M, 71	Brainstem infarct	+	Convergence failure	Attenuated	No effect	Not done
5	M, 24	Granuloma of mesencephalon, sarcoid	+	Enhanced	Attenuated	No effect	Prone and supine—upbeat abolished
6	M, 53	Wernicke's encephalopathy	+	No effect	No effect	No effect	Supine—suppressed
7	F, 60	Unknown	+	Convergence failure	No effect	No effect	Supine—no effect Prone—not done
8	M, 22	Head injury	+	Convergence → torsional	No effect	Abolished on left gaze	Supine and prone—abolished
9	F, 40	Multiple sclerosis	+	Enhanced	No effect	No effect	Supine—enhanced Prone—abolished
11	F, 24	Tuberculoma	+	Convergence failure	Not done	No effect	Supine—diminished Prone—enhanced

Pursuit defects Upward pursuit was absent in all patients Downward pursuit was hypometric in Cases 1, 2, 3 and 4, absent in Cases 5, 7 and 11, and normal in Cases 6 and 8 + = nystagmus obeyed Alexander's Law, — = it did not

Case 1. Diagnosis: Ependymoma of the Fourth Ventricle—Postoperative

Following the removal of a fourth ventricular ependymoma a 42-year-old man experienced oscillopsia in the vertical plane. Examination revealed third degree upbeat nystagmus which was enhanced on up and down gaze and by convergence. Pursuit in the vertical plane was impaired in both directions. The responses to whole field optokinetic stimulation in the vertical plane were deranged. Oscillation in pitch in the light about the axis of pitch produced responses consistent with superimposition of the upbeat nystagmus on the vestibulo-ocular reflex (VOR), that is, the responses appeared hypometric with the head becoming prone and hypermetric with the head becoming supine. Static tilt to the supine position exaggerated the nystagmus. When he was 30 deg prone the nystagmus was abolished (fig. 1).

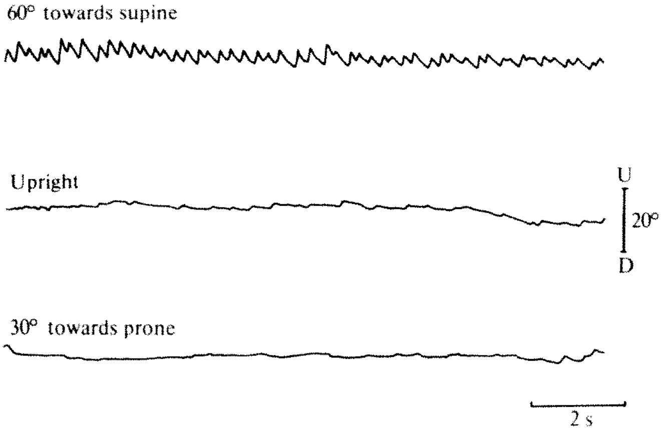

FIG. 1. Electro-oculographic recordings of movements of the right eye in the vertical plane taken from a patient with an ependymoma of the fourth ventricle (*Case 1*). The records illustrate the differential effects upon upbeat nystagmus of static tilt of the head with respect to gravity into the prone and supine positions. U = upwards; D = downwards.

Case 2. Diagnosis: Possible Multiple Sclerosis

A 34-year-old woman who three years earlier had been noted to have an internuclear ophthalmoplegia after a closed head injury developed diplopia and unsteadiness. On examination there was third degree upbeat nystagmus which was enhanced on lateral gaze and in darkness. In the vertical plane, pursuit movements upwards were absent and were impaired downwards. Optokinetic stimulation using a small drum enhanced the nystagmus with the drum moving downwards but with the drum moving upwards the upbeat nystagmus was attenuated. In the horizontal plane there was bilateral internuclear ophthalmoplegia; pursuit and optokinetic responses (OKN) to full field stimulation were deranged in both directions. Romberg's test produced increased sway with eye closure and she veered to the left when walking with her eyes closed. Hallpike's manoeuvre exaggerated the upbeat nystagmus with either ear dependent. The clinical diagnosis of multiple sclerosis was supported by bilaterally abnormal visual evoked potentials and the presence of oligoclonal IgG bands in the CSF.

Case 3. Diagnosis: Brainstem Infarction

A 60-year-old man, who had previously had mitral and aortic valve replacements, presented with an acute onset of vertical oscillopsia, intermittent diplopia, vertigo and unsteadiness. On examination there was a third degree upbeat nystagmus which was enhanced by fixation on a target and abolished by convergence. Static tilt to the prone and supine positions abolished the upbeat nystagmus. In the vertical plane pursuit was deranged in both directions but less so when following downwards. Large field optokinetic stimulation produced exaggeration of upbeat nystagmus with downward movement and some direction reversal (that is, downbeat nystagmus) with upward movement. Oscillation about the axis of pitch in the light demonstrated a normal VOR with the head moving down and a hypermetric VOR with the head moving up. In the horizontal plane there was bilateral gaze-evoked nystagmus, saccadic pursuit, absent vestibulo-ocular reflex suppression and full and symmetrical OKN. Caloric and rotational responses were reduced and consistent with bilateral drug-induced vestibular toxicity. Romberg's test was negative although he veered to the left when walking with eyes closed. A CT brain scan demonstrated cerebral atrophy.

Case 4. Diagnosis: Brainstem Infarction

A 71-year-old hypertensive man was admitted for investigation following several transient ischaemic attacks characterized by vertigo, bilateral amaurosis, diplopia, quadriparesis, anarthria, and confusion. On examination there was a second degree upbeat nystagmus which changed to downbeat nystagmus on downward gaze. The upbeat nystagmus was attenuated in darkness. Pursuit in the vertical plane was abnormal but more so for upward following. In the horizontal plane there were bilateral internuclear and partial supranuclear ophthalmoplegias, absent pursuit, essentially normal OKN in response to full field stimulation (allowing for the internuclear ophthalmoplegia) and impaired vestibulo-ocular reflex suppression. There was convergence failure (although pupillary constriction was observed) and bilateral lid retraction. A CT brain scan revealed calcification in the basilar artery and the right terminal carotid artery as well as an infarct in the anterior portion of the left corona radiata. Three months later all the oculomotor abnormalities had resolved.

Case 5. Diagnosis: Granuloma of the Mesencephalon, Probable Sarcoidosis

A 35-year-old male Indian presented with a two month history of left sided paraesthesiae, dysarthria, weight loss and impotence; in the month prior to consultation he had developed progressive left-sided weakness. On examination he had a left hemiparesis and impairment of sensation. There was a first degree vestibular nystagmus to the left and third degree upbeat nystagmus. On positional testing with either ear dependent, there was downbeat nystagmus which became a left beating

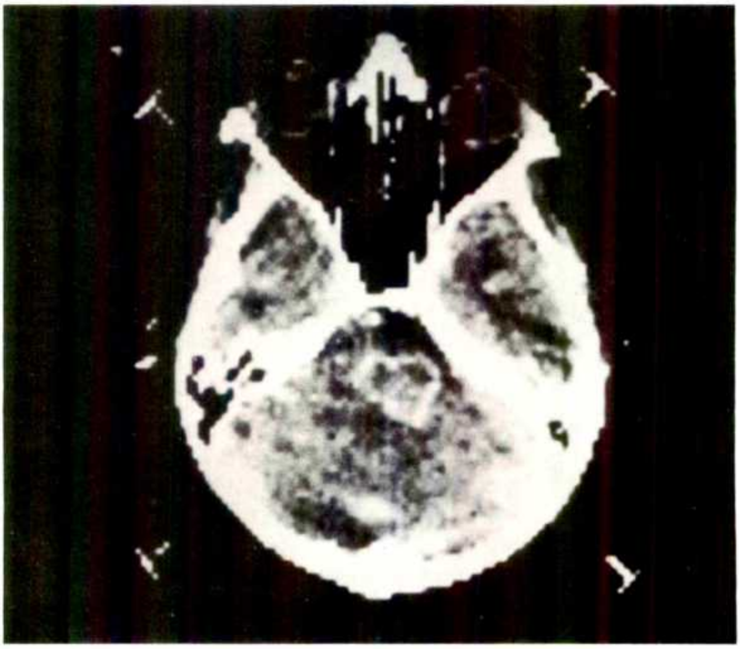

FIG. 2. CT scan (horizontal plane) showing enhancement of a mixed attenuation, intrinsic lesion with a crenellated edge at the pontomesencephalic junction (*Case 5*).

nystagmus when the upright posture was resumed. The positional nystagmus was of immediate onset and did not fatigue. Optokinetic responses were disorganized and of low amplitude in all planes. The peak angular velocity of 30 deg displacement horizontal saccades was reduced to the order of 20 to 80 deg/s. Smooth pursuit was absent. Static tilt abolished the upbeat nystagmus which was replaced by a third degree right beating nystagmus. The CT scan showed a contrast-enhancing intrinsic lesion at the level of the pontomesencephalic junction ventral to the aqueduct (fig. 2). CSF was normal apart from a protein of 0.1 g/l. Biopsy of a nodular skin lesion on the left buttock showed a noncaseating giant cell granuloma. The patient was treated with corticosteroids and antituberculous therapy and the abnormalities resolved. No definitive diagnosis was made.

Case 6. Diagnosis: Wernicke's Encephalopathy

A 53-year-old man was admitted to hospital with a seven day history of frequent falls. During the three weeks before his referral he had been drinking heavily. General examination showed an enlargement of the liver. On neurological examination he was mildly disorientated in time but not place, had bilateral sixth nerve palsies and a severe truncal ataxia. Whilst seated he had an upbeating nystagmus in primary gaze. There was no change on upgaze but the amplitude diminished on downgaze. The nystagmus was unaltered by removal of fixation. The peak angular velocity of downward saccades was greatly reduced. Upward pursuit was absent whilst downward pursuit was normal. Optokinetic stimulation with upward movement of the stimulus resulted in intermittent suppression of the upbeat nystagmus during which the eyes remained quite still. OKN downwards was hyperactive. Vertical vestibulo-ocular reflexes during voluntary head oscillation in pitch appeared normal. A CT scan showed a well defined peripheral infarction in the inferior half of the left cerebellar hemisphere. There was associated moderate bifrontal and superior vermis atrophy. Laboratory studies confirmed the presence of thiamine deficiency. The cranial nerve palsies resolved and his gait improved on treatment with thiamine. Ten weeks later he died from a perforated diverticulum of the sigmoid colon.

At autopsy, in addition to an old infarct of the cerebellum, the mamillary bodies were brown and shrunken with an appearance typical of chronic Wernicke's encephalopathy. Histologically there was cell loss, gliosis and an increased number of small blood vessels in the mamillary bodies, dorsomedial nuclei of the thalamus, the inferior colliculi, the ventral tegmental nuclei of the midbrain and pons and the lateral segments of the midbrain reticular formation. There was pallor in the mamillary bodies and mild loss of Purkinje cells in the anterior superior vermis and cell loss in the dentate nuclei. There was almost total loss of neurons in the dorsomedial segments of the inferior olive with proliferation of the glial elements.

Case 7. Aetiology Unknown

A 60-year-old woman was referred for a further neurological opinion because of persistent complaints of dizziness, blurred vision and ataxia. She had a past history of psychiatric disturbance but had received no drugs for some months. Eye movement examination revealed second degree upbeat nystagmus. Vertical pursuit movements were severely impaired. In the horizontal plane there were square wave jerks with bilateral 'gaze evoked' nystagmus, poorly formed disorganized OKN with full field stimulation in both directions, bidirectionally deranged pursuit and impaired vestibulo-ocular reflex suppression. The responses to caloric irrigation of the ears were normal apart from failure of fixation suppression. She displayed a consistent mild cerebellar ataxia. A CT brain scan showed an enhancing lesion on the right side of the posterior fossa with the appearances of a petrous ridge meningioma. However, as this was small and not producing any apparent mass effect, it was disregarded. The patient refused any further investigations and a diagnosis was not made.

Case 8. Diagnosis: Head Injury

A 22-year-old man suffered a head injury when rolled upon by his horse. He was unconscious for 24 h and sustained a hairline fracture of the frontal bone. Subsequently he complained of double vision with a separation of images along an oblique axis which was constant for all positions of gaze. In addition he had an illusion of the world slipping upwards which was exacerbated by head movements in the vertical plane. On examination three months after the accident he had total failure of accommodation and vergence. He had a comitant exotropia and his pupillary responses to light were sluggish. There was a third degree upbeat nystagmus which was present also on right gaze but replaced by torsional nystagmus on left gaze. Pursuit upwards was absent but downwards it was normal for target velocities greater than the slow phase velocity of the upbeat nystagmus. Pursuit in the horizontal plane was hypometric. The VOR for head movement downwards was hyperactive and for head movement upwards was hypoactive. The nystagmus was abolished by tilting to the prone and supine positions. Optokinetic responses to upward movement were absent but were intact for downward movement. It was concluded that his failure of vergence was attributable to periaqueductal mesencephalic lesion.

Case 9. Diagnosis: Multiple Sclerosis

A 40-year-old female was admitted with a seventeen day history of unsteadiness, vertigo and blurring of vision. In the previous eleven years she had had recurrent episodes of sensory disturbance involving all four limbs, each lasting about three months, and one episode of visual impairment in the left eye. On neurological examination there was a slurring dysarthria, slight left facial weakness, moderate ataxia of the limbs, greater on the left, and a mild spastic paraparesis. The neuro-otological findings were primary position upbeat nystagmus, enhanced on convergence and in the supine position; its amplitude was diminished when the patient was prone. Pursuit was absent in the vertical plane as was optokinetic nystagmus. Vestibulo-ocular reflex suppression was grossly impaired. In the horizontal plane pursuit was hypometric. The upbeat nystagmus had disappeared when the patient was seen two months later and her ataxia had improved.

Case 10. Diagnosis: Focal Demyelination of the Medulla

A 32-year-old Indian woman presented with a one month progressive history of hiccoughs, vomiting without nausea, dysphagia and dysarthria. On admission she was afebrile. There was upbeat nystagmus in the primary position of gaze and first degree nystagmus to the right. Upward pursuit was absent. Further testing was impossible because of persistent vomiting. In addition there was impaired tonsillar fossa sensation, partial paralysis of the palate, greater on the left, and inability to protrude the tongue. In the limbs there was a mild left-sided intention tremor. Extensive investigations failed to elucidate the nature of the patient's illness. The CSF contained a maximum of 234 mononuclear cells/mm^3 one week after admission and the protein was elevated at 1.24 g/l. Oligoclonal IgG bands were first detected one month after admission. The CSF became normal within seven weeks, apart from the persistence of oligoclonal bands. In the week following her admission she deteriorated with loss of ability to breathe whilst asleep, developed a mild bilateral facial weakness and following a metrizamide CT scan became quadriplegic. At this point she lost her upbeat nystagmus. Over the next six months she had recurrent chest infections and died of a fulminating bronchopneumonia.

At autopsy the only lesion found in the CNS was an extensive area of demyelination, with some axonal loss, in the floor of the fourth ventricle extending from just below the sixth nerve nuclei to the low medulla (fig. 3).

Case 11. Diagnosis: Possible Tuberculoma

Over a four week period a 24-year-old Indian woman developed progressive diplopia and ptosis. She felt generally unwell and on admission had a fever. There was a pleural effusion and biopsy confirmed caseating tubercles. Neurological examination demonstrated a minimal facial weakness. All other signs were confined to the eye movements. There was a bilateral ptosis, the left greater than the right. In primary gaze the right eye was exotropic with complete failure of adduction. There was a partial failure of upward gaze. When the patient was upright or lying prone she had an upbeating nystagmus in the

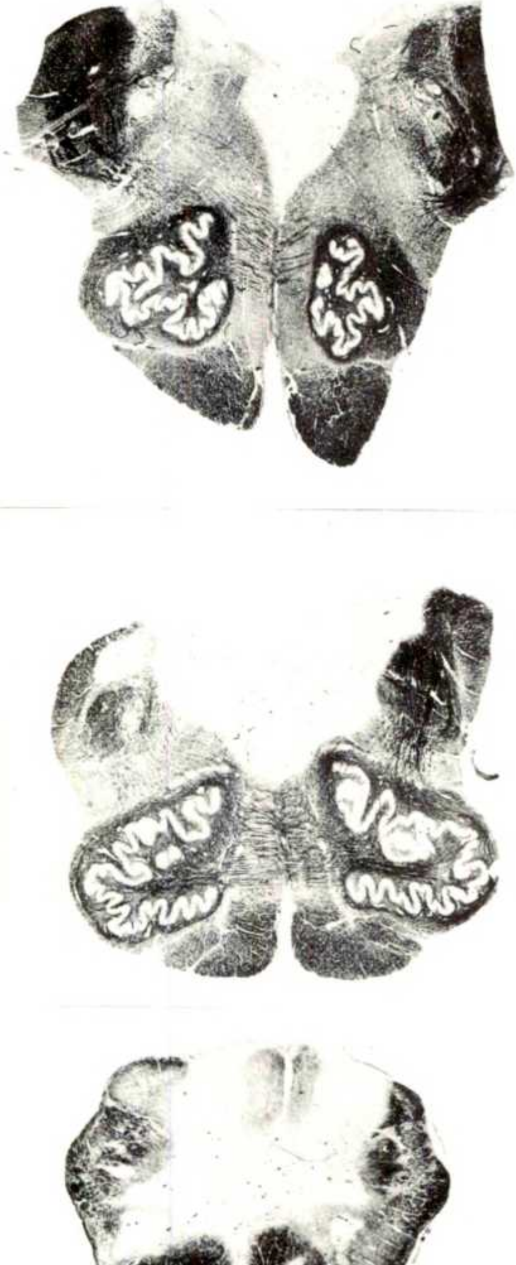

FIG. 3. Sections of medulla from pontomedullary junction (*above*) to the decussation of the pyramids (*below*) showing extensive demyelination (*Case 10*). Luxol fast blue stain.

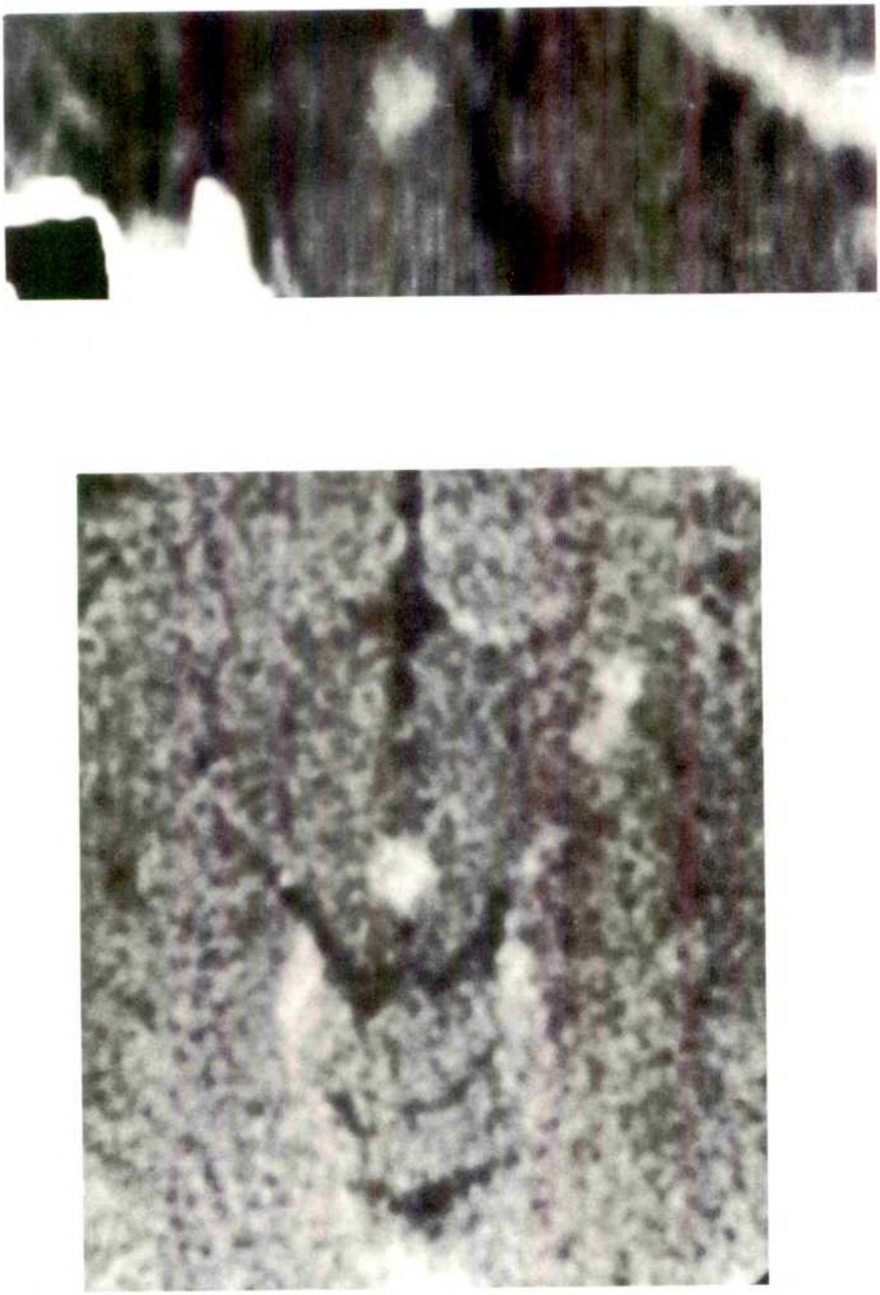

FIG. 4. CT scans of a small enhancing lesion at the pontomesencephalic junction (*above*, sagittal plane; *below*, horizontal plane) (*Case 11*).

primary position of gaze. When lying supine the upbeat nystagmus was abolished and she developed a downbeat nystagmus which was evoked by slight depression of the eyes. Saccades in all directions were slow. There was no smooth pursuit in any direction. Downward optokinetic responses were absent. The CT scan demonstrated a small enhancing lesion at the pontomesencephalic junction (fig. 4). The CSF was entirely normal.

DISCUSSION

Site of Lesions Associated with Upbeat Nystagmus

The earliest clear description of upbeating nystagmus is by Stengel (1935) who attempted to define the site of the responsible lesion. He tentatively ascribed the nystagmus to lesions of the central tegmental tracts of the pons. Unfortunately his patient, who had diabetes mellitus, had several areas of degeneration in the CNS in addition to those in the pons. Later reports in which unequivocal pathology is available implicate the same general region. Thus O'Brien and Bender (1945) described a single case associated with thrombosis of the anterior spinal artery of the medulla. Upbeat nystagmus following drainage of an abscess in the ventrolateral pons 2 mm rostral to the pontomedullary junction was observed by van Gilder *et al.* (1974). Schatz *et al.* (1975) reported upbeat nystagmus with a 'discrete' metastatic neoplasm involving the medulla but did not give a precise localization. Gilman *et al.* (1977) analysed the nystagmus in a patient with a low grade astrocytoma involving the inferior olive, medullary tegmentum, inferior and middle cerebellar peduncles and caudal pons. Histologically the tumour had infiltrated the medial longitudinal fasciculus bilaterally, the perihypoglossal nuclei and all vestibular nuclei. Upbeat nystagmus in association with a diffuse astrocytoma of the brainstem, thought on radiographic examination to involve principally the mesencephalon, was reported by Troost *et al.* (1980). Brandt and Büchele (1983) reported upbeat nystagmus in a patient in whom the CT scan revealed a tumour at the pontomesencephalic junction. The localization and extent of the lesion were similar in our Case 5.

Upbeat nystagmus in alcoholic degeneration has been described several times, for example by Bender and Gorman (1949) and Cox *et al.* (1981). These reports indicate that the nystagmus occurs in degenerations of the cerebellum, inferior olive or central tegmental structures. The diffuse nature of these processes, however, usually precludes accurate anatomical localization. There is only one report, to our knowledge, of upbeat nystagmus associated with an intrinsic cerebellar lesion (adenocarcinoma). Pathology confirmed that the lesion was restricted to the left cerebellar hemisphere, dentate nucleus and brachium conjunctivum and, upon microscopic examination, brainstem lesions were absent (Nakada and Remler, 1981, Case 1). The authors ascribed the nystagmus to an asymmetry of vertical canal function due to interruption of pathways running in the brachium; however, no neuro-otological tests were performed which would support this hypothesis. There is no evidence from isolated focal lesions that upbeat nystagmus arises in association with pathology of the anterior cerebellar vermis as proposed by Daroff and Troost (1973).

In the present series, lesions at two sites were associated with upbeat nystagmus, namely the pontomedullary and the pontomesencephalic junctions. In Cases 5 and 11 there were large but well circumscribed lesions at the pontomesencephalic junction. These findings are in accord with those in the case reported by Troost *et al.* (1980) but provide a more precise localization. Similar support is given by the findings of advanced degeneration and gliosis in the ventral tegmental nuclei of the midbrain and lateral segments of the midbrain reticular formation in our Case 6.

On the other hand Case 10 of the present series shows that lesions in the floor of the fourth ventricle at and below the pontomedullary junction can be associated with upbeat nystagmus. Clinically this patient presented with a lesion in the region of the vagal nuclei which spread rapidly to involve the other bulbar cranial nerves and ultimately the facial nerve and long tracts, at which point she lost her upbeat nystagmus. At autopsy an extensive lesion involving the floor of the fourth ventricle was found and this included the perihypoglossal nuclei. Our patient with an ependymoma of the fourth ventricle (Case 1) also points to the same area, in accord with the observations of van Gilder *et al.* (1974). Thus the weight of evidence for localization derived from the literature, together with our cases, indicates two principal areas associated with the generation of upbeat nystagmus, namely the central tegmentum at the pontomedullary junction (5 cases) and the pontomesencephalic junction (3 cases). It is also possible that cerebellar lesions can provoke upbeat nystagmus. Any correlation between the behavioural characteristics of upbeat nystagmus and the occurrence of lesions at these sites would be significant and of interest.

The known oculomotor structures likely to be involved in the production of upbeat nystagmus at the pontomedullary junction are the perihypoglossal nuclei (Baker *et al.*, 1982). The location of these nuclei corresponds with the site of the lower brainstem lesions associated with upbeat nystagmus. Abnormalities of the proposed integrating function of the perihypoglossal nuclei could account for the slow phase component of the nystagmus. Furthermore, the occurrence of upbeat nystagmus in the presence of an intact primary vestibulo-ocular reflex and of normal saccadic eye movements indicates that the major pontomedullary oculomotor structures are functionally intact.

The origin of upbeat nystagmus in association with high brainstem lesions at the pontomesencephalic junction is more obscure. In one previous case (Troost *et al.*, 1980) it was suggested that interruption of pathways leading to cell groups in the mesencephalic reticular formation could produce a selective upward bias on oculomotor neurons similar to that proposed as the basis for 'pursuit defect nystagmus' (Zee *et al.*, 1974). An alternative hypothesis is that there is an interruption of connections between the integrators of the pontine paramedian reticular formation and of the mesencephalic reticular formation that are known to be of importance for gaze holding in the vertical plane (Lang *et al.*, 1982). If this is so, the cause of upbeat nystagmus could be similar for both proposed sites of lesions.

The Effects of Convergence

Carl *et al.* (1982) reported 4 cases of downbeat nystagmus and one case of upbeat nystagmus in which convergence had similar effects. A slow phase velocity bias in the upward direction was produced which enhanced the downbeat nystagmus and in the case of upbeat nystagmus reversed the direction. Cox *et al.* (1981) reported another case of upbeat nystagmus in whom convergence converted the nystagmus to downbeating. In both papers the findings were used as evidence in support of theories concerning the organization of the oculomotor system and the mechanism of vertical nystagmus. These speculations derive from a model for vertical downbeating nystagmus proposed by Zee *et al.* (1974) which was extended to include upbeating nystagmus by Mehdorn *et al.* (1979). This model suggests that there are separate neural integrators for up and down gaze which receive input from the pursuit, saccadic and vestibular systems. The integrators act in a push/pull fashion so that a defect in pursuit in one direction may give rise to nystagmus in that same direction. It was suggested that the patient with upbeat changing to downbeat nystagmus on convergence had a relative deficit of upward pursuit at distance and of downward pursuit for near vision.

The fact that 3 of the patients in the present study had upbeat nystagmus exaggerated by convergence, and in 2 cases it was suppressed, is evidence against Cox's theory and would suggest that the interactions between the eye movement systems are more complex than was hitherto suspected.

The Effects of Tilt

In a recent report of a case of downbeat nystagmus we demonstrated that the nystagmus was increased by tilting the patient into any position away from that of normal upright posture (Chambers *et al.*, 1983). In the present study static tilt influenced upbeat nystagmus in 7 out of 11 patients and in the remainder testing was incomplete. The variability of the effects of static tilt on the upbeat nystagmus were different in each patient suggesting that there were variations in pathophysiology. However, the fact that in most instances upbeat nystagmus was influenced by tilt implies that the abnormal mechanism responsible for the nystagmus is strongly influenced by otolith stimulation. In those cases in which the upbeat nystagmus appears to depend solely upon tilt, in the absence of asymmetrical canal or pursuit mechanisms, it is parsimonious to propose that the nystagmus arises from an imbalance of otolith influences on oculomotor function.

The effects of convergence on upbeat nystagmus may also be related to the involvement of otolith influences. If the otoliths have a role in generating compensatory eye movements in response to linear, translational motion of the head (which is an open question in the physiological literature), then the otolith control should have different gain characteristics for near as opposed to far targets. This becomes evident if the geometry of the situation is considered. If, for example, the eyes are fixated in the far distance and the head moves vertically up and down through a displacement of a few centimetres (a motion encountered particularly during riding at the trot), then no compensatory eye movements at all are required for the maintenance of visual stability of the target. This observation derives from the Euclidean axiom that parallel lines meet at infinity. In contrast, during similar motion, if the visual axes are to be stabilized on a near target, perhaps a few centimetres away, then a compensatory movement of the eyes is necessary. The relationship determining the amount of eye movement is approximately an inverse function of the angle whose tangent is target distance/head displacement. Because the tangent relationship increases rapidly with increasing distance of the target, compensatory eye movements of significant amplitude should only be produced for targets which are quite close to the head. At these distances convergence is a significant factor in the alignment of the visual axes and one would expect that it should interact with otolith-mediated compensatory eye movements. Thus we propose that the effects of convergence on upbeat nystagmus can be derived from the interaction of otolith and vergence control of oculomotor mechanisms.

Canal mediated, vestibulo-ocular reflexes also have gain characteristics which are modified by convergence. It is possible that in our cases of nystagmus which were affected by convergence, additional asymmetries of vertical canal function were provoked by the vergence movement. However, an otolith mediated compensatory eye movement should only occur when the eyes are fixated on relatively near targets. In contrast, canal reflexes occur with both near and far fixation. Thus there is a strong reason for proposing that vergence-otolith interaction is responsible for the striking effects of convergence on upbeat nystagmus, particularly in the absence of other signs of abnormal vertical canal function.

With the notable exception of ocular counter-rolling, behavioural studies on normal subjects have failed to demonstrate vertical eye movements of any significant velocity resulting from natural otolith stimulation (*see* Miller, 1962; Young *et al.*, 1981). In contrast, physiological studies in animals have demonstrated that the otoliths exert a distinct action on the extraocular muscles responsible for vertical and torsional movement (Precht *et al.*, 1979).

There are two possible reasons for the negative findings in the human experiments. First, the possible influence of convergence upon otolith-ocular reflexes, as discussed above, appears to have been overlooked in the investigation of otolith function. Secondly, it is difficult to provide linear motion of the head at frequencies (above 1 Hz) necessary to obviate a contribution from pursuit reflexes to compensatory eye movements without also causing the subject unacceptable discomfort or inducing angular motion of the head. In contrast, the evidence from pathophysiology is that the otolith or its central connections can have a strong influence on eye movements (Halmagyi *et al.*, 1980; Chambers *et al.*, 1983). Since the evidence derived from pathological states shows that abnormal otolith function can have a profound effect upon eye movements then it would be surprising if the otoliths did not have some role in normal oculomotor control.

Relationship with Pursuit and the VOR

The findings relating to pursuit, vestibular and optokinetic reflexes do little to resolve the controversy between the two current theories of the origin of nystagmus in the vertical plane. The 'vestibular' theory (Baloh and Spooner, 1981) postulates that vertical nystagmus arises from an uncompensated asymmetry, at a central level, of vestibular tonus. A sign of the failure of compensatory mechanisms is the accompanying absence of a smooth pursuit reflex. The alternative explanation of vertical nystagmus is the 'pursuit defect' theory (Zee *et al.*, 1974) described above.

There is evidence that asymmetrical pursuit did not generate upbeat nystagmus in most of our cases. Measurements of pursuit performance in either direction showed that it was equally deranged in the majority of our patients when the presence of a slow phase downward eye movement was taken into account. The nystagmus in Case 9 was totally absent when she was prone so that pursuit could be assessed without the contamination of the slow phase of upbeat nystagmus. When measured in this position her pursuit was deranged equally in either direction. Hence it is doubtful that a postulated asymmetry of pursuit mechanisms, which should be equal in both upright and prone positions, could be contributing to the generation of the nystagmus slow phase.

The alternative vestibular theory which proposes that there is an imbalance between vertical canal systems is not supported by our data. The asymmetry of the vertical 'dolls head' reflexes observed in our patients are simply explained in terms of summation of the slow phase of the upbeat nystagmus and a normal reflex from the vertical canals (e.g. Case 1). Thus it is not necessary to propose further abnormalities of canal function to explain the behaviour of upbeat nystagmus in the present series.

In the other cases of upbeat nystagmus the origin of the slow phase component remains obscure. Any mechanisms that might be proposed to explain the slow eye movement responsible are conjectural.

Symptomatology of Upbeat Nystagmus: Relationship with Oscillopsia, Vertigo and Postural Instability

The question arises as to whether the oculomotor abnormalities observed in our patients occur as an isolated phenomenon or part of a more generalized vestibular defect. In 4 of our patients the signs did seem to be confined to the oculomotor system, implying that the physiological abnormality causing upbeat nystagmus can occur in isolation. On the other hand, in the remaining patients there was evidence of axial or limb ataxia but clearly this is not a necessary part of the syndrome. It is curious that only 3 of our patients complained of oscillopsia. This is in marked contrast to patients with downbeat nystagmus in whom oscillopsia is a frequent complaint. In addition to oscillopsia, 2 of these patients complained of vertigo in the sense of a 'whirling' sensation as did one patient who did not experience oscillopsia. Thus upbeat nystagmus can occur in the presence or absence of a whole spectrum of disorders of balance and its presence does not necessarily imply that there will be other features of a vestibular disturbance.

Relationship with Positional Nystagmus of the 'Central Type'

Cawthorne and Hinchcliffe (1961) distinguished between nystagmus which was present on normal upright posture and modified by tilt and nystagmus which appeared only on tilting. The term 'positional nystagmus of the central type' was reserved for this latter variety. In contrast, earlier authors, particularly Nylen (1931) grouped both together, considering them to be variants, and this view was adopted by Hallpike (1962). Our view, in the light of experience gained in studying the behavioural characteristics of upbeat and downbeat nystagmus, is that all nystagmus in which sensitivity to tilt is a dominant feature should be subsumed under the classification of central positional nystagmus. It is unfortunate that although earlier authors recognized that nystagmus of the vertical (or torsional) variety is frequently sensitive to tilt, in the post-1940s literature, this characteristic is often overlooked. Perhaps for this reason, erroneous or incomplete theories of the genesis of vertical nystagmus have appeared.

CONCLUSIONS

The variations in amplitude of upbeat nystagmus in response to static tilt in the majority of patients we have surveyed indicates that the generation of the nystagmus is strongly influenced by otolith stimulation. This factor has not been taken into account in previous reports of patients with this form of nystagmus. Formerly upbeat nystagmus has been ascribed to defects of pursuit or vertical canal function; the evidence for these latter mechanisms in the present series is uncertain.

The clinical importance of primary position upbeat nystagmus lies in the fact that the majority of reported cases involve an intra-axial lesion of the tegmental grey matter at the pontomesencephalic and pontomedullary junctions. From the literature there is evidence that intrinsic cerebellar lesions, probably involving the brachium conjunctivum, can also give rise to primary position upbeating nystagmus. However, in these cases, it is not known how the nystagmus is influenced by vestibular stimulation.

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LIVEDO RETICULARIS AND CEREBROVASCULAR LESIONS (SNEDDON'S SYNDROME)

CLINICAL, RADIOLOGICAL AND PATHOLOGICAL FEATURES IN EIGHT CASES

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SUMMARY

Eight patients with diffuse livedo reticularis and cerebrovascular lesions (Sneddon's syndrome) are reported. The disorder was inherited by autosomal dominant transmission in 3 cases. Multiple occlusions in medium-sized arteries were demonstrated by cerebral and hand arteriograms. Digital artery biopsies showed intimal hyperplasia in 7 cases and recanalized thrombosis in one case. Our findings are compared with an extensive review of the literature. Differential diagnosis with other vascular disorders, especially cerebral thromboangiitis obliterans and the corticomeningeal angiomatosis of Divry and Van Bogaert is considered. We conclude that Sneddon's syndrome is a new genetic and progressive arteriopathy, occlusive and noninflammatory, involving medium-sized vessels. The pathogenesis has yet to be elucidated.

INTRODUCTION

Sneddon's syndrome is a rare entity characterized by idiopathic livedo reticularis (LR) and cerebrovascular lesions (Sneddon, 1965; Piñol Aguadé *et al.*, 1975; Rumpl and Rumpl, 1979; Quimby and Perry, 1980; Thomas *et al.*, 1982). The nature and pathogenesis of this association remain unclear. On the basis of the lesions found in the dermal arterioles on skin biopsy in some cases, Sneddon (1965) considered that the underlying arteriopathy was a type of endarteritis obliterans. The same type of pathology in dermal arterioles is also mentioned by Piñol Aguadé *et al.* (1975) and Quimby and Perry (1980). Postmortem examination in one case (Piñol Aguadé *et al.*, 1975) revealed widespread endarteritis obliterans affecting small and medium-sized arteries.

In this study, we present the clinical, genetic, radiological and pathological findings in eight patients with idiopathic LR and cerebrovascular lesions. The hospital serves a population of 500,000. During the period of the study (January 1977 to December 1981) a diagnosis of cerebrovascular disease (WHO rubric numbers 430 to 438) was made in 3006 patients. In this series the cases of Sneddon's syndrome therefore represent 0.26 per cent of the total cerebrovascular disease cases.

PATIENTS AND METHODS

We have studied 8 patients with diffuse idiopathic LR and cerebrovascular lesions. The following laboratory data were obtained in all cases: full blood count, erythrocyte sedimentation rate, routine urinalysis, serum electrolytes, calcium, phosphorus, blood urea nitrogen, fasting blood sugar, uric acid, bilirubin, alkaline phosphatase, LDH, SGOT, SGPT, CK, creatine clearance, lipid profile, amylase, serum protein electrophoresis, luetic serology, platelet function studies and coagulation profile, antinuclear antibody, LE cell preparations, rheumatoid factor, cryoglobulins, hepatitis-associated antigen, total haemolytic complement, C_3, circulating immune complex determinations, cerebrospinal fluid (CSF) examination (cells, protein, sugar, VDRL, protein immunoelectrophoresis and IgG levels), ECG and cardiological study, standard EEG, skull and chest x-rays, hand and cerebral angiography, CT cranial scan and skin and digital artery biopsies.

Digital arteriography was performed by puncturing the brachial artery percutaneously just above the antecubital fossa, using a 16-gauge needle directed distally. The patients fasted for 8 h prior to the procedure and received 50 mg of meperidine hydrochloride. Twenty millilitres of Radialar-280 (Meglumine diatrizoate 60 per cent) was injected intra-arterially, using an automatic injector at a rate of about 5 ml/s. The film sequence extended over a period of 20 s, exposing 1 frame every 2 s. Diluted papaverine hydrochloride (20 mg) was then injected into the catheter and immediately after, a repeat contrast medium study was performed.

The following stains were used in the skin biopsies: haematoxylin and eosin (H and E), Masson trichrome, PAS, and orcein stain for elastic tissue. Segments of digital artery were obtained by an incision on the medial side of the fourth finger at the level of the proximal interphalangeal joint. The artery was isolated from surrounding structures and a short segment of the vessel was then excised. Sections of the artery were processed for histology and stained with H and E, PAS, orcein, and oil red O. Other sections were stained by toluidine blue. Immunofluorescent studies were performed on skin and digital artery biopsies using monospecific conjugate antisera to IgG, IgM, IgA, IgE, IgD, C_{1q}, C_3, fibrinogen and albumin.

RESULTS

Clinical Features

Sex, age and initial symptoms. There were 7 women and 1 man (Case 7), their ages ranging from 18 (Case 1) to 59 (Case 7) years (mean, 46). Age at onset ranged between 10 (Case 8) and 33 (Case 3) years (mean, 19). Initial symptoms were LR (Cases 1–4 and 6–8) and stroke (Case 5).

Cutaneous signs. Extensive LR was a constant and progressive sign, involving all four limbs and the trunk (fig. 1); it was severe in Cases 2, 3, 5, 7 and 8, and moderate in Cases 1, 4 and 6. The livedo worsened in cold weather and during the acute phase of the neurological deficits. In none of the cases were there ulcerations or cutaneous nodules. With the exception of Case 5, LR preceded the neurological symptoms by several years.

Peripheral ischaemic manifestations. All the patients had early, but not severe, signs of chronic ischaemia in the extremities. These were acroerythrocyanosis,

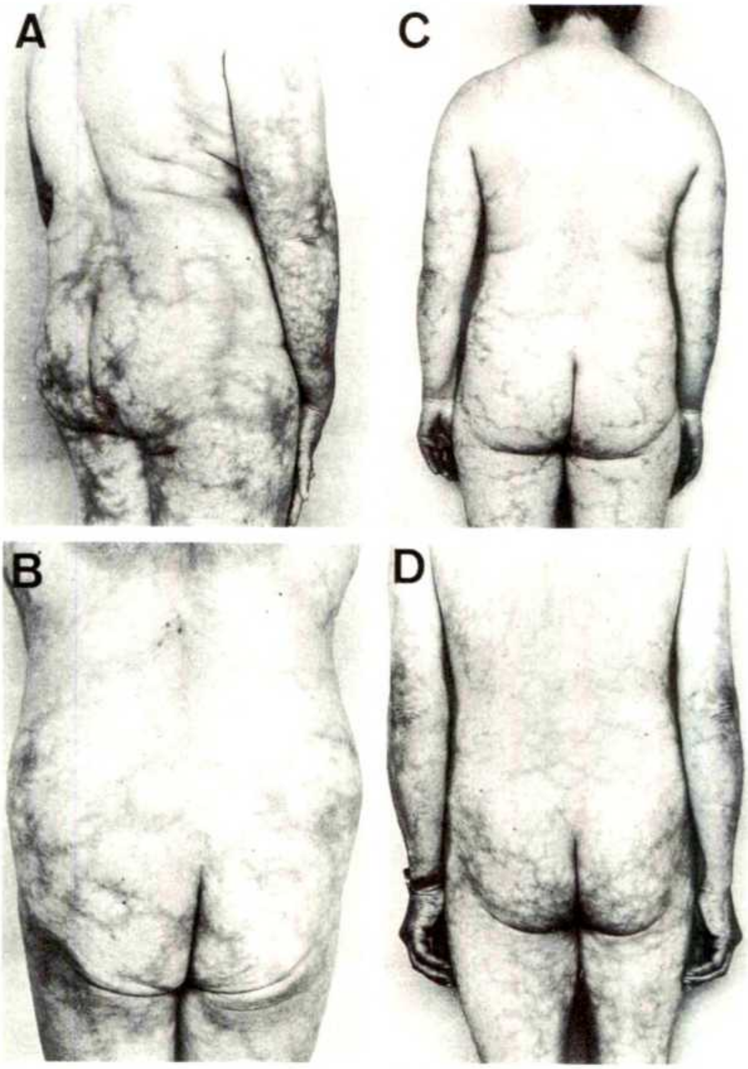

FIG. 1. Extensive livedo reticularis. A, Case 2; B, Case 5; C, Case 8; D, Case 7.

coldness of hands and feet, impaired or absent arterial pulsations in posterior tibial and dorsalis pedis arteries, and typical Raynaud's phenomenon in 5 cases (1, 4, 6–8).

Arterial hypertension. Six patients had mild hypertension which was easily controlled by temporary diuretic treatment and a sodium-restricted diet.

Neurological manifestations. These consisted of strokes (Cases 1–5 and 8), transient ischaemic attacks (Case 6), epileptic seizures (Cases 2 and 7) and progressive dementia (Cases 2–5). Each patient suffered a minimum of two strokes, the first always occurring before the age of 45 years. The strokes were of limited

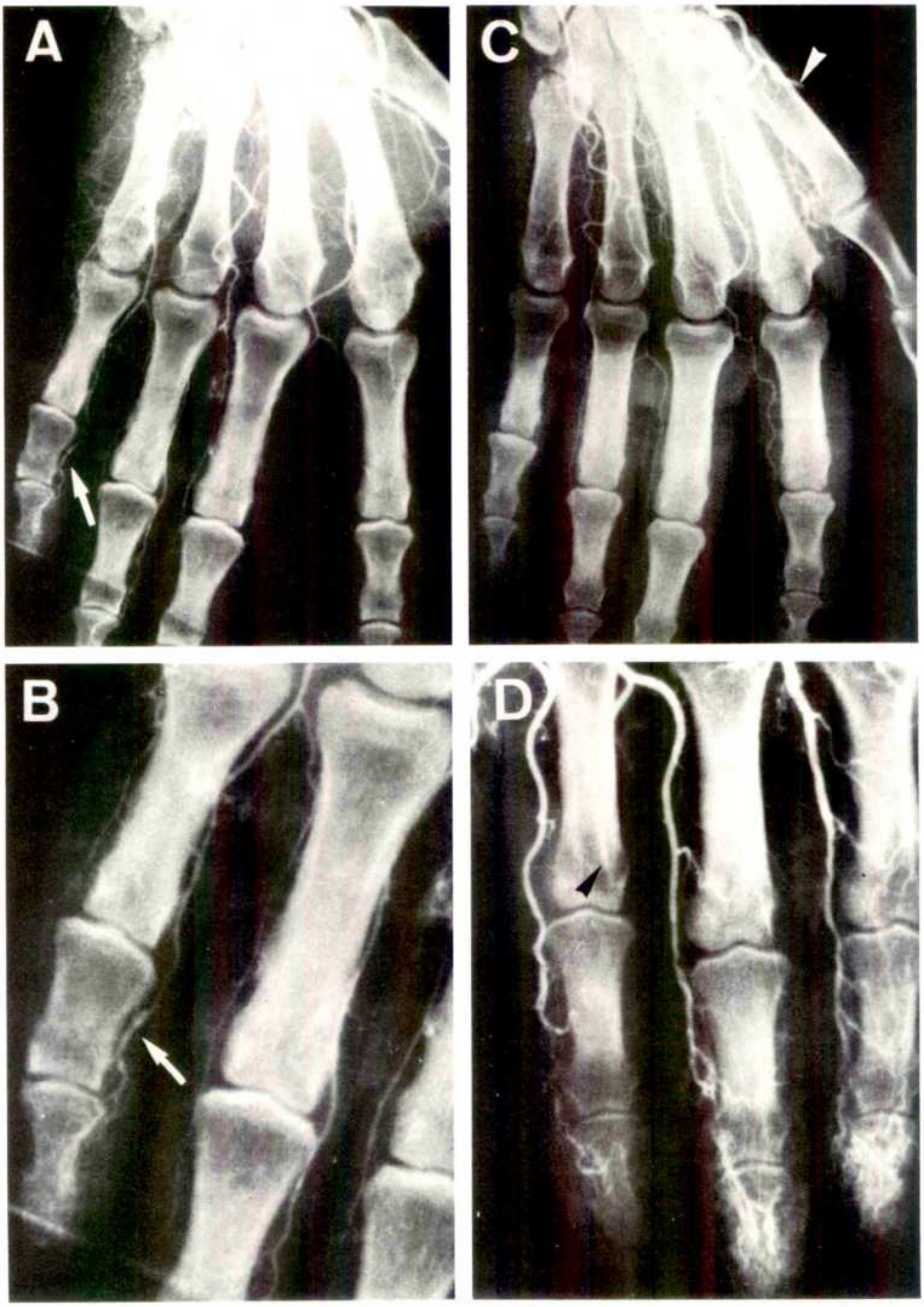

FIG. 2. Hand arteriograms illustrating widespread narrowing and irregularity (arrows) of the lumina of the digital arteries with several sites of apparently total obstruction (arrowheads). A, B, Case 2; C, Case 6; D, Case 4.

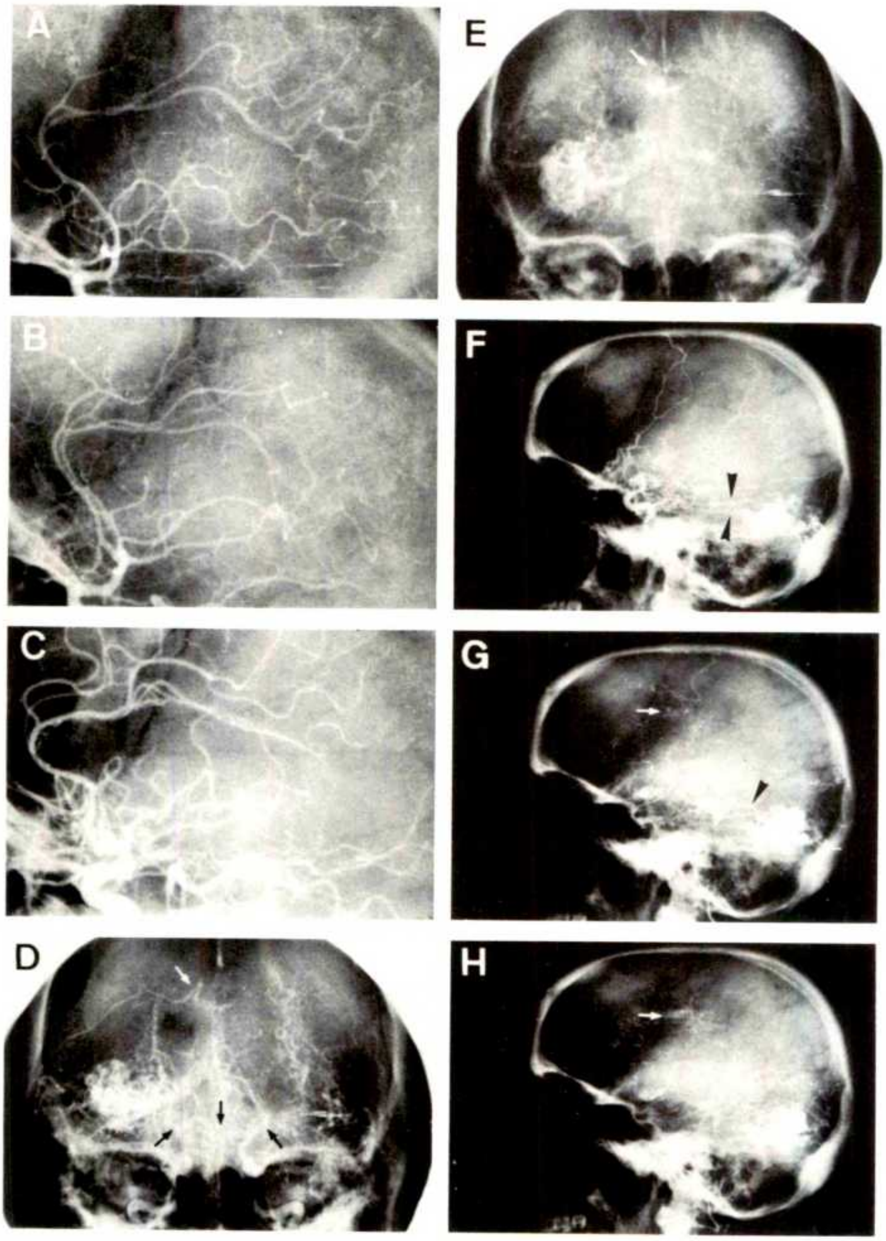

FIG. 3. A–C, carotid angiograms showing narrowing and occlusions in the distal segments of opercular branches and distal pericallosal artery (A, B, Case 2; C, Case 3). Simultaneous left carotid and right retrograde brachial angiography (D, E) and right retrograde brachial angiography (F–H) in Case 4, showing complete occlusion of both anterior and middle cerebral arteries (black arrows) and arteriovenous malformation in the right occipital lobe supplied by the tentorial branch of the carotid artery and meningeal branches of the occipital and middle meningeal arteries (black arrowheads). A collateral network is visible bilaterally in the base of the brain; a large network of fine collateral vessels is also seen in the subcortical regions (E). Prominent transdural anastomoses are seen in the pericallosal region (white arrows).

extent, leaving little residual deficit. The predominant signs and symptoms were hemiparesis, central facial paresis, aphasia and hemianopia, and less frequently hemihypesthesia, paraesthesiae and pseudobulbar dysarthria. Mental deterioration began in each case after the first stroke, being severe in Cases 2 and 4.

Radiological Features

Hand angiography. This was abnormal in all cases. The changes observed in the angiograms were segmental narrowing and dilatation in the common and proper palmar digital arteries, together with multiple obstructions and marked reduction in calibre located mainly in the latter (fig. 2).

Cerebral angiography. This was also abnormal in all 8 patients. The changes can be divided into three groups (fig. 3): (1) obstructions and stenosis located in the distal (Cases 1, 2 and 5–8) or basal (Cases 3 and 4) branches of the intracranial arteries; (2) collateral circulation in the brain which included transdural anastomoses (Cases 2, 4, 5 and 8), anastomoses between intracranial arteries (Cases 3, 4 and 6)

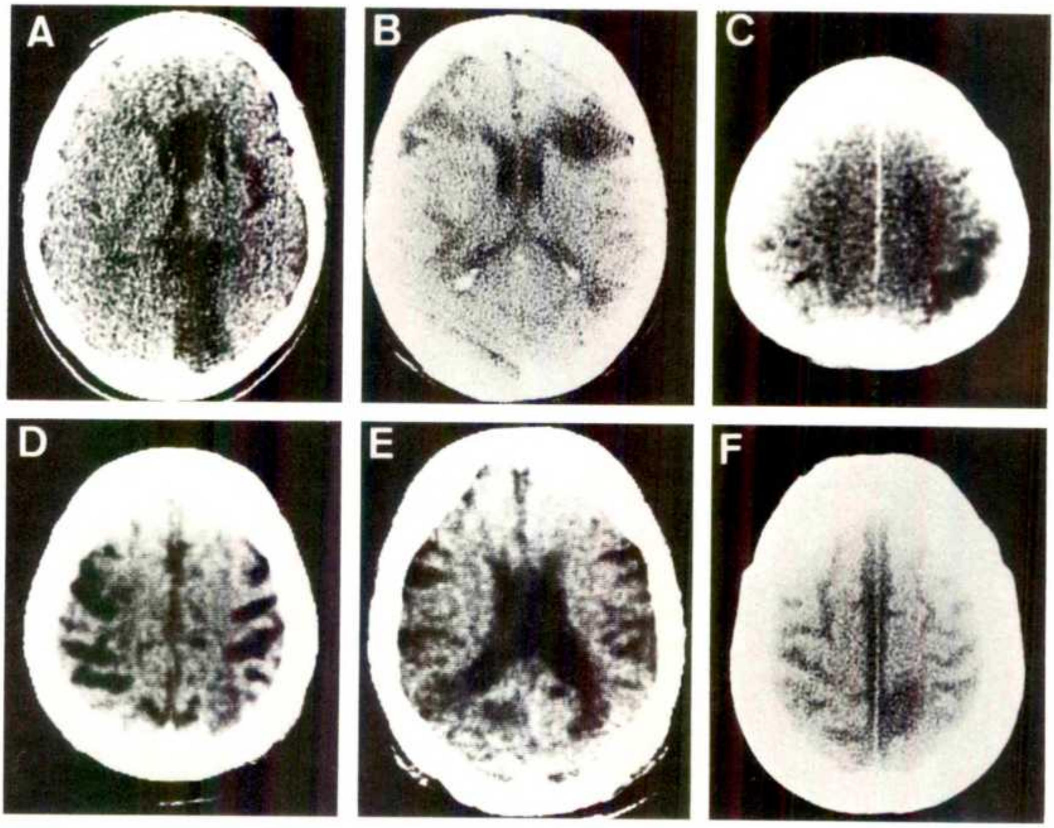

FIG. 4. CT scan findings. A, Case 3; B, Case 5; C, Case 7; D, E, Case 2; F, Case 4. Multifocal brain infarcts (A, B), focal brain atrophy (C) and diffuse cortical atrophy with associated infarcts (D–F).

and 'moyamoya' type anastamoses *via* the deep perforating vessels at the base of the brain (Cases 3 and 4); and (3) an intracranial arteriovenous malformation in Case 4.

Cerebral CT scan (fig. 4). Focal areas of low density were seen in all the patients except Case 6. There were two or more in Cases 2–5. A constant finding was a variable degree of cortical atrophy with ventricular dilatation. Postcontrast studies carried out in Cases 1, 2 and 6–8 did not provide further information.

Histopathological Findings

Skin biopsies were normal in all cases.

Digital artery biopsies (fig. 5, Table). In 7 patients there was focal, segmental intimal hyperplasia. The intimal tissue consisted mainly of fibroelastic proliferation with small numbers of intimal smooth-muscle cells. The internal elastic lamina, except for isolated zones of focal absence or reduplication, appeared to be well preserved. The medial coat of these arteries was normal, but the tunica adventitia

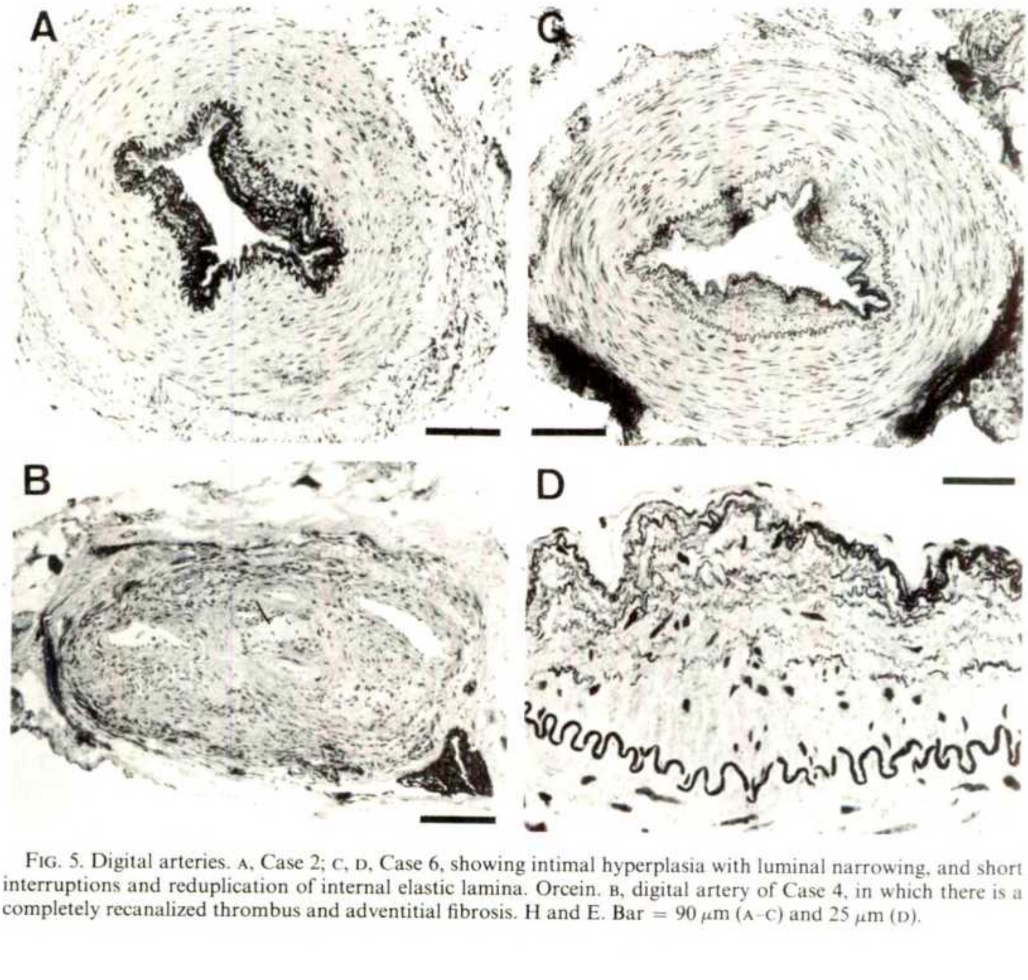

FIG. 5. Digital arteries. A, Case 2; C, D, Case 6, showing intimal hyperplasia with luminal narrowing, and short interruptions and reduplication of internal elastic lamina. Orcein. B, digital artery of Case 4, in which there is a completely recanalized thrombus and adventitial fibrosis. H and E. Bar = 90 μm (A–C) and 25 μm (D).

showed slight fibrosis. In Case 4, the artery was completely occluded by old thrombus which was organized and recanalized. We found no evidence of either acute or chronic inflammation, fibrinoid necrosis or lipid deposits, and immunofluorescent studies were negative in all cases.

TABLE. PATHOLOGICAL FINDINGS IN DIGITAL ARTERIES

Case No.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Age (yrs) and sex	*18, F*	*44, F*	*49, F*	*53, F*	*57, F*	*52, F*	*59, M*	*33, F*
Intimal thickening*	2+	3+	3+	—	3+	3+	3+	3+
Percentage luminal narrowing	30	40	35	—	40	40	40	40
Alteration of the IEL	Focal reduplication	No	No	Total	No	Focal absence	No	No
Adventitial fibrosis*	1+	2+	1+	1+	1+	1+	1+	1+
Thrombosis	—	Mural	—	Recanalized	—	—	—	—
Alteration of the media	—	—	—	Atrophy	—	—	—	—

* These abnormalities were graded according to the following scale: 1+ = minimal; 2+ = mild and 3+ = moderate. IEL = internal elastic lamina.

Other Laboratory Data

The remainder of the laboratory studies were normal or irrelevant.

Genetic Data

In Case 1 (fig. 6A), a great aunt, aged 51 years, has had a diffuse LR since she was young, in addition to hypertension, strokes and dementia in the last few years. However, examination of the parents and siblings of the proposita was normal. Genetic data in Case 2 are given in detail below. In Case 7 (fig. 6B), according to information obtained from the patient and her family, the father and one of the six sisters had generalized LR. In the remaining patients, the family history was negative.

In order to illustrate the above mentioned characteristics of the disease process, one case is described in detail.

Case 2 (II-1 in fig. 6C)

A 44-year-old right-handed woman was admitted in October 1977 with mental deterioration, focal neurological symptoms and epileptic seizures. At the age of 16 years, she developed diffuse and progressive LR. Four years later, acroerythrocyanosis and erythema pernio in winter were added, but she did not have Raynaud's phenomenon. At the age of 35 years, the patient suffered a sudden attack of left hemiparesis and dysarthria. There was rapid and complete recovery from the neurological deficits with the exception of slightly dysarthric speech. Later, progressive mental deterioration was observed and she became dependent on her family at the age of 41 years. Repeated convulsive attacks controlled by phenytoin and phenobarbitone occurred from the age of 36. At 44 years, she suffered a further transient attack with left hemiparesis. Sphincter control was normal.

On examination, blood pressure was 140/90, there was acroerythrocyanosis and marked generalized LR, mainly of axial distribution (fig. 1A). Pulsation was weak in the left posterior tibial artery and absent in the left dorsalis pedis artery. Neurological examination revealed an inattentive patient with

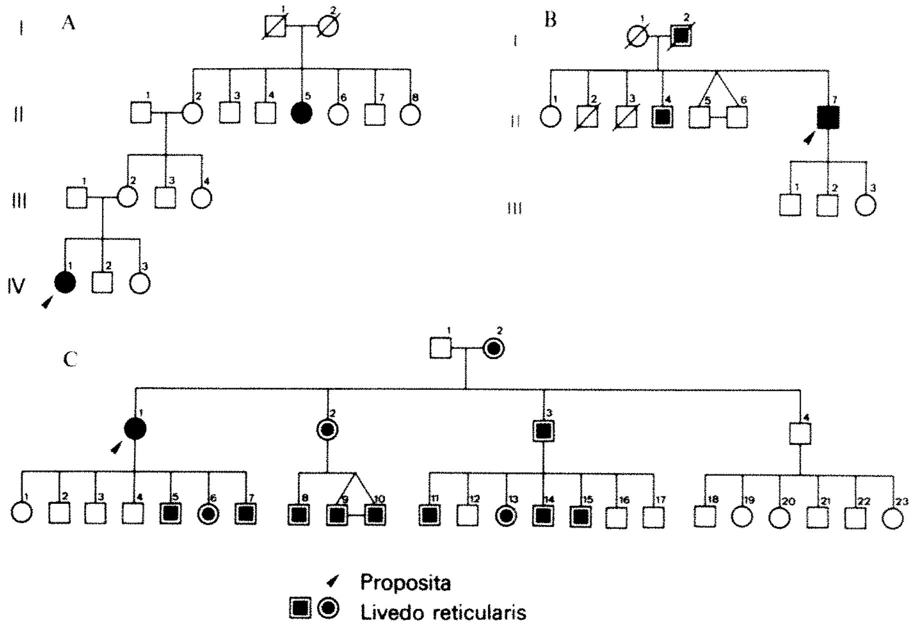

FIG. 6. Pedigrees of Cases 1 (A), 7 (B) and 2 (C).

lack of inhibition and emotional lability. She was orientated, but there was a marked loss of recent memory and immediate recall. A severe pseudobulbar dysarthria and reduced spontaneous speech were noticeable. There was agraphia, alexia, constructional apraxia, inability to calculate and errors of judgement. There was an incomplete left homonymous hemianopia. There was slight hypertonus in all four limbs and all the tendon reflexes were exaggerated. The plantar reflexes were equivocal.

Repeated EEGs showed focal theta activity in both temporoparietal regions. Figs. 2A, B, 3A, B and 4D, E record the radiological findings in this patient, and fig. 5A shows the histopathological changes in the digital artery.

Course. In December 1980, the patient developed hypertension (190/120) and her dementia increased; she was treated with a sodium-restricted diet and chlorthalidone 50 mg daily. At present the patient takes phenobarbitone and antiplatelet drugs (aspirin 250 mg and dipyridamole 300 mg daily) and is clinically stable.

Family history. We have examined 28 members of this family and found that 13 had LR (fig. 6C). Two brothers of the proposita (Cases II-2 and II-3) and one of her nieces (Case III-13) also had acroerythrocyanosis, erythema pernio or Raynaud's phenomenon. Hand angiography in Case II-2 showed similar findings to the proposita. A CT scan in Cases II-3, III-11 and III-13 were normal.

DISCUSSION

The clinical features in our patients are similar to the 18 cases described under the heading 'LR and cerebrovascular lesions' or 'Sneddon's syndrome' (Champion and Rook, 1960; Church, 1962; Sneddon, 1965; Trzebicki and Buksowicz, 1969; Piñol Aguadé *et al.*, 1975; Rumpl and Rumpl, 1979; Quimby and Perry, 1980; Thomas *et al.*, 1982; Stephens and Ferguson, 1982). We have excluded reports with clinical manifestations similar to those of Sneddon's syndrome but without adequate clinicopathological evidence (Barker *et al.*, 1941, Cases 7 and 8), or published as cerebral thromboangiitis obliterans (Sträussler *et al.*, 1937; Davis and Perret, 1947; Meyer, 1948; Geyer, 1961; Sunder-Plassmann and Isfort, 1962; Gambetti *et al.*, 1966; Pellat *et al.*, 1976; Arnott *et al.*, 1977, 1979) or post-traumatic cranial syndrome (Herman and Sulat, 1959).

The male:female ratio is 1:7 in our series and 9:9 in previously published cases; however, a clear female prevalence such as we have observed was also found in Sneddon's series (1965), in which 5 out of 6 patients were women.

The average age when diagnosis was made was 46 years in our patients and 41 years in previously reported cases, while the average ages of onset of symptoms were approximately 19 and 35, respectively. LR was the first symptom in the majority of patients in both series, usually preceding the neurological symptoms by several years. The livedo was always diffuse and progressive, and frequently worsened during the acute phase of the neurological symptoms; it was never found in association with ulceration or cutaneous nodules.

In three of our cases (Cases 1, 2 and 7) the disease, either in its clinical entirety or with LR as the only clinical manifestation, was inherited. In the family of Case 1, the disease is apparently transmitted as a dominant autosomal character with incomplete penetrance, and the family pedigree of Case 2 corresponds fully to what is to be expected in a simple autosomal dominant transmission. In the family of Case 7 the transmission of LR from father to sons suggests once more an autosomal dominant mode of inheritance. To our knowledge, hereditary diffuse LR has only been reported in corticomeningeal angiomatosis of Divry and Van Bogaert (Divry and Van Bogaert, 1946; Baro, 1964) and in cutis marmorata telangiectatica congenita (Kurczynski, 1982), inheritance being autosomal recessive or dominant.

Ischaemic strokes, usually repeated, were by definition a constant manifestation in the cases in the literature and also in our series, except for Case 7, in whom, however, a CT scan revealed multiple infarcts. As Sneddon himself stated (1965), the strokes were of limited extent, frequently leaving little residual deficit. In addition, sporadic transient ischaemic attacks have been observed (Case 6 in our series; Piñol Aguadé *et al.*, 1975, Cases 2 and 3; Rumpl and Rumpl, 1979; Stephens and Ferguson, 1982, Cases 1 and 2). The repeated ischaemic strokes led to dementia in Cases 1 and 2 of Stephens and Ferguson (1982) and in our Cases 2–5; furthermore, mental deterioration was the first manifestation in the case of Trzebicki and Buksowicz (1969). Epileptic attacks occasionally occur in the advanced stages of the disease (Case 2 in our series; Sneddon, 1965, Case 3; Piñol Aguadé *et al.*, 1975, Case 3; Rumpl and Rumpl, 1979; Thomas *et al.*, 1982, Case 1) and as an exception they constitute the only neurological manifestation (Case 7 in our series).

Signs and symptoms of peripheral ischaemia as observed in our series are rarely mentioned (Champion and Rook, 1960; Quimby and Perry, 1980). This probably reflects the lack of importance of these clinical manifestations. Hypertension was found in 6 of our patients (Cases 1, 2 and 5–8) and in 12 of the published cases

(Champion and Rook, 1960; Church, 1962; Sneddon, 1965, Cases 1, 2, 4 and 6; Rumpl and Rumpl, 1979; Quimby and Perry, 1980; Thomas *et al.*, 1982, Cases 1 and 2; Stephens and Ferguson, 1982, Cases 1 and 3). The hypertension was almost always of benign type, with no renal change of significance. In one case (Sneddon, 1965, Case 1), more severe hypertension was found with hypertensive fundal changes of grade 3 type, but a good recovery was made with hypotensive drugs.

Cerebral angiography was undertaken in 7 of the 18 cases published; in 3 of them it was reported to be normal (Sneddon, 1965, Case 1; Piñol Aguadé *et al.*, 1975, Case 2; Rumpl and Rumpl, 1979) and in the remaining 4 (Sneddon, 1965, Case 2; Trzebicki and Buksowicz, 1969; Piñol Aguadé *et al.*, 1975, Case 1; Quimby and Perry, 1980) it showed multiple occlusions in the distal branches of the cerebral arteries, as in our Cases 1, 2 and 5–8. Moreover, we often saw instances of collateral circulation of the brain consisting of transdural anastomoses, anastomoses between intracranial arteries, or anastomoses *via* the deep perforating vessels at the base of the brain (moyamoya type); judging by their figs. 2 and 3, the latter patterns of replacement supply are also evident in the case of Trzebicki and Buksowicz (1969). Arteriovenous malformations, as observed in our Case 4, have not been reported previously in Sneddon's syndrome. In the cases where a cranial CT scan was carried out (Rumpl and Rumpl, 1979; Quimby and Perry, 1980; Thomas *et al.*, 1982, Cases 1 and 2; Stephens and Ferguson, 1982, Cases 1 and 3) it showed, as in our patients, the existence of a variable degree of cortical atrophy and isolated or multiple areas of infarction; these findings are closely correlated with the clinical and angiographical data.

Arteriographic investigations have been used to evaluate the arteries in the hands of patients with peripheral ischaemic manifestations (Porter *et al.*, 1976; Rodnan *et al.*, 1980). Multiple narrowing and obstruction of the digital arteries after preliminary administration of vasodilators to prevent vascular spasm were observed in our patients. These findings have also been described in many patients with Raynaud's phenomenon of various aetiologies (Rodnan *et al.*, 1980) and Buerger's disease (Juergens, 1980), including the cerebral variety of thromboangiitis obliterans (Pellat *et al.*, 1976; Arnott *et al.*, 1979; Biller *et al.*, 1981), but not in the reported cases of Sneddon's syndrome. As might be expected from these angiographic findings, the biopsies of the digital arteries constantly revealed obstructive lesions consisting of intimal hyperplasia (7 cases) or a recanalized thrombosis. Inflammatory changes indicative of arteritis were not found in any patient. In the only case of Sneddon's syndrome who came to postmortem examination (Piñol Aguadé *et al.*, 1975, Case 1) a musculoelastic intimal hyperplasia diffusely located in medium-sized arteries was also found. Intimal hyperplasia of medium-sized arteries is not a specific lesion, and has been shown to occur in relation to multiple pathological factors (Rinaldi *et al.*, 1976; Irey *et al.*, 1978; Rodnan *et al.*, 1980) and in advancing age (Laws *et al.*, 1967). The thrombosis present in the digital arteries of Case 4 was probably secondary to the initial endarteriopathy. As in our cases, the skin biopsies that have been reported were normal or showed nonspecific changes (Church, 1962;

Sneddon, 1965; Piñol Aguadé *et al.*, 1975, Cases 2 and 3; Rumpl and Rumpl, 1979; Thomas *et al.*, 1982, Cases 1 and 2; Stephens and Ferguson, 1982, Case 1), although the presence of endarteritis obliterans in dermal arterioles has been noted occasionally (Champion and Rook, 1960; Trzebicki and Buksowicz, 1969; Piñol Aguadé *et al.*, 1975, Case 1; Quimby and Perry, 1980).

The differential diagnosis of Sneddon's syndrome should include a large number of conditions that are capable of giving rise to diffuse LR with systemic arterial involvement (Champion, 1965; Champion and Wilkinson, 1968; Ryan, 1976). The most relevant are atherosclerosis, diseases with intravascular occlusion and systemic vasculitis (Fan *et al.*, 1980). Our clinical, pathological and laboratory data allow us to exclude them. However, in the neurological literature there are two processes, Divry-Bogaert disease (Divry and Van Bogaert, 1946; Van Bogaert and Martin, 1971; Julien *et al.*, 1971) and cerebral thromboangiitis obliterans (CTAO) with diffuse LR (Sträussler *et al.*, 1937, Case 2; Lindenberg and Spatz, 1939, Case 1; Davis and Perret, 1947, Case 7; Meyer, 1948, Cases 2, 10, 14 and 19; Geyer, 1961, Case 1; Sunder-Plassmann and Isfort, 1962, Cases 1–4; Gambetti *et al.*, 1966; Pellat *et al.*, 1976; Arnott *et al.*, 1979), which are difficult to differentiate from Sneddon's syndrome. The clinical picture in these three processes is similar. Cerebral and/or hand angiographies in CTAO (Geyer, 1961, Case 2; Sunder-Plassmann and Isfort, 1962, Cases 1, 3 and 4; Gambetti *et al.*, 1966; Pellat *et al.*, 1976; Arnott *et al.*, 1979) and cerebral angiography in a case of Divry-Bogaert disease (Julien *et al.*, 1971) showed similar findings to those observed in our cases. Postmortem studies in CTAO with LR (Sträussler *et al.*, 1937, Case 2; Lindenberg and Spatz, 1939, Case 1; Davis and Perret, 1947, Case 7; Meyer, 1948, Cases 2, 10, 14 and 19; Gambetti *et al.*, 1966; Pellat *et al.*, 1976; Arnott *et al.*, 1979) have revealed lesions in medium-sized arteries similar to those described by us in digital arteries, but without the inflammatory changes characteristic of Buerger's disease. As these cases do not fulfil the minimal criteria for the diagnosis of Buerger's disease (McKusick *et al.*, 1962; McPherson *et al.*, 1963; Goodman *et al.*, 1965; Shionoya, 1975; Juergens, 1980) without which CTAO is excluded (Biller *et al.*, 1981; Drake, 1982), we suggest that CTAO with diffuse LR and Sneddon's syndrome are probably one and the same process. Postmortem examination in cases of Divry-Bogaert disease have shown meningeal angiomatosis, multifocal infarcts and parietal thickening of the leptomeningeal arteries with thrombosis and recanalization (Divry and Van Bogaert, 1946; Baro, 1964; Van Bogaert and Martin, 1971). The existence of these occlusive arterial lesions together with the finding of a moyamoya syndrome in two of our patients leads us to question whether this leptomeningeal capillary network represents a true angiomatosis or a hypervascularization of the surface of the brain as described in the moyamoya syndrome (Smith *et al.*, 1968; Poór and Gács, 1974; Picard *et al.*, 1974; Coakham *et al.*, 1979; Haltia *et al.*, 1982).

The classification of Sneddon's syndrome has not been well established; in fact, it is not mentioned either in neurological texts in common use (Aita, 1972; Stehbens, 1972; Yates, 1976; Adams and Victor, 1981) or in studies on cerebrovascular diseases (Millikan, 1975; Golden, 1978). Sneddon himself considered that this vascular disorder was 'a type of endarteritis obliterans perhaps similar to Takayasu's arteriopathy' (Sneddon, 1965). Our findings indicate that this process is a new genetic and progressive arteriopathy, of occlusive and noninflammatory type, involving medium-sized vessels. Its pathogenesis has yet to be clarified.

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STEREOTAXIC THALAMOTOMY IN 55 CASES OF DYSTONIA

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SUMMARY

The results of stereotaxic thalamotomy in 55 cases of dystonia are presented. The 16 cases with generalized dystonia were of varied pathogenesis, only 7 being typical of the idiopathic form of adolescent onset. Four of the 16 cases benefited considerably, but the others showed little or no lasting improvement. These results are in contrast to those obtained by Cooper (1976).

Of the 27 cases with segmental or focal dystonia, 22 had spasmodic torticollis; 16 of these had bilateral thalamotomies, and 62 per cent were much improved. The incidence of operative complications, in particular dysarthria, was high following bilateral lesions.

The incidence of hemiparesis, known to have persisted for more than a year, was 15 per cent. This complication was as frequent in those with unilateral as with bilateral thalamotomies. The incidence of dysarthria in those without preoperative bulbar dystonia was much higher in those who had bilateral lesions (56 per cent) as compared with those who had unilateral lesions (11 per cent).

The group that has been identified as benefiting greatly from stereotaxic surgery comprises those with hemidystonia following unilateral brain damage. In these patients, symptomatic improvement in abnormal movement is striking and the incidence of operative side effects from unilateral lesions is low.

INTRODUCTION

Torsion dystonia is a descriptive term for a disorder of movement and posture characterized by muscle spasms, which may be intermittent or continuous. If the muscle spasms are confined to a localized group of muscles, such as an arm, the condition is referred to as focal dystonia (FD). If the abnormality extends to involve a body segment, for example the neck and upper limbs, the condition is referred to as segmental dystonia (SD). The most unpleasant and distressing form of torsion dystonia is generalized dystonia (GD), when all four limbs and the trunk are distorted by muscle spasms. Torsion dystonias can be symptomatic or idiopathic. Idiopathic generalized torsion dystonia, known as dystonia musculorum deformans (DMD), is a condition that afflicts young people, particularly children of Ashkenazi Jewish origin, and causes painful and crippling muscle spasms of the whole body.

Although a growing weight of evidence (Fahn, 1976) suggests that torsion dystonias are due to an imbalance of amine metabolism in the basal ganglia and therefore potentially correctable by drugs, the disorders have proved singularly resistant to medical treatment. A moderate relief of symptoms has been claimed for treatment by benzodiazepines, anticholinergics, and carbamazepine (Marsden and Fahn, 1982*a*). In one particular group of patients, who have a marked diurnal fluctuation in their symptoms of dystonia, L-DOPA has been of considerable benefit (Segawa *et al.*, 1971). In addition, relaxation therapy has been applied to dystonias of limited distribution (Korein and Brudny, 1976) with claims for modest success.

There have been occasional reports of amelioration of dystonic symptoms in a proportion of cases, following stereotaxic thalamotomy (Markham and Rand, 1961; Riechert, 1962; Bertrand *et al.*, 1979; Marsden, 1981). The largest series is by Irving Cooper who has operated on 227 patients with DMD, often with dramatic improvement (Cooper, 1976).

We describe here the results of stereotaxic thalamotomy in 55 cases of torsion dystonia, both idiopathic and symptomatic. The efficacy of thalamotomy in the different types of dystonia is analysed.

METHODS

A retrospective study of the cases was carried out by examining the notes of all patients with torsion dystonia in whom stereotaxic thalamotomy had been performed. There were 55 patients, mostly referred from neurologists in the London region. Fifteen came from abroad.

Stereotaxic thalamotomy was performed at the Middlesex Hospital and the Regional Neurosurgical Centre, Oldchurch Hospital, Romford, Essex, between the years 1964–1982, by one of the authors (J.A.). Patients were referred for neurosurgery when all diagnostic investigations had been completed and usually when exhaustive medical treatment had failed. When a patient had been recently investigated at the referring hospital, preoperative investigations were confined to ascertaining the size of the ventricular system by computerized x-ray tomography or on a preoperative air encephalogram.

Anatomical studies of the anatomy of nuclei within the thalamus have shown that the following relationships exist (Andrew and Watkins, 1969). Using a modification of Hassler's terminology (Hassler *et al.*, 1979), the posterior boundary of Vim (ventralis intermedius) lies immediately anterior to Vce (ventralis caudalis externus), the sensory relay nucleus for the limbs and trunk, and is in the same coronal plane as the anterior limit of Vci (ventralis caudalis internus), the sensory relay nucleus for the face. In 1 mm slices through the thalamus, the anterior border of Vci is easily identified by the naked eye and is found to lie between 11 and 15 mm posterior to interventricular foramen (Andrew and Watkins, 1969). The variability in the distance of Vci behind the foramen is shown in fig. 1. Since precision is critical in siting targets for lesions and there is such variability in the position of nuclear boundaries, it is important to identify thalamic nuclei by electrophysiological means as an adjunct to calculations based on stereotaxic reference points.

The staged procedure we used for stereotaxic thalamotomy was as follows. Under general anaesthesia, contrast medium was injected into the ventricular system and a multiperforated sphere, held between metal cups, fixed into the vault of the skull near the coronal suture. This was aligned so that a wide area of the thalamus could be examined electrophysiologically at the second operation. A measuring probe was inserted through the sphere to the estimated target point and check x-rays were taken so that the precise distance of the probe tip from the reference plane and reference points was known.

A few days later, under local anaesthetic where possible, the second stage was carried out. Using a bipolar electrode of the type described by Albe-Fessard (Albe-Fessard *et al.*, 1966) connected to an audiovisual display unit, recordings were made to determine the location of muscle stretch responses in the posterior part of Vim and the anterior part of the sensory relay nucleus. Evoked cutaneous responses from Vci and Vce were obtained more posteriorly. When it was not possible to monitor cell activity, electrical stimulation was used to judge the position of the sensory relay nuclei. Using a monopolar electrode with the remote electrode on the scalp, an alternating current at a stimulating voltage of 0.5–2 at 50 to 100 Hz was applied for a few seconds. If the electrode was very close to the internal capsule then a low current would produce a myoclonic jerk. Similarly, if the electrode was in the sensory relay nucleus the patient would complain of pins and needles down the opposite side.

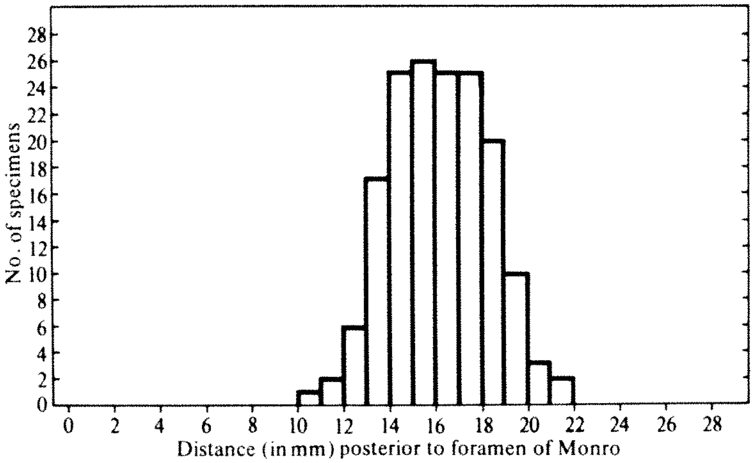

FIG. 1. Frequency distribution of the distance of the nucleus ventralis caudalis internus from the interventricular foramen (Andrew and Watkins, 1969). Reproduced by permission of Williams and Wilkins Co.

Based on the physiological delineation of nuclear positions, the parameters for the target sites were calculated, and lesions made accordingly. An electrode with a thermocouple at the tip was heated to 66° C for 150 s, using a radiofrequency current. This created a circumscribed area of necrosis in the shape of an oblate spheroid with a length of 6 mm and a maximum diameter of 3 to 4 mm (Watkins, 1965).

In cases of GD we usually made three lesions, Vim, Vce-Vci and CeM (centromedian nucleus) on the first side, in one session. An interval of between a few days to some months, depending upon the development of any postoperative complications, was necessary before operating on the opposite side. Lesions made on the second side were spaced at intervals of some days since operative side effects appeared to be cumulative. The target sites were the same as those on the first side. In 3 patients with GD, who did not respond to bilateral lesions, additional lesions were made in the pulvinar, as described by Cooper (Cooper *et al.*, 1974). In hemidystonia, lesions in CeM were not usually necessary.

Postoperatively the patients remained in the neurosurgical unit until they could be discharged or returned to the referring hospital. Patients were then followed in the neurosurgical outpatient clinic or by the referring hospital. The follow-up records of those patients who returned abroad immediately were usually poor.

Postoperative assessment was made for each of four time periods: (1) postoperatively prior to discharge; (2) up to one year; (3) over one year; and (4) over three years. For each time period a 'disability score' was assigned. When a patient had not returned to the neurosurgical clinic, late follow-up information was obtained either by writing to the patient, to a relative, the general practitioner or the referring physician.

When examining the case records, special attention was given to the following points. Since the causative agent could rarely be identified and the diagnosis was necessarily a descriptive term, all information concerning the clinical picture and presumed pathogenesis was sought. The age of onset of symptoms, duration of illness and age at the time of operation was noted. The disability from dystonia in the preoperative and the four postoperative epochs was scored. The score ranged from 1 (socially disabled) to 7 (bedridden). In between, 2 = mildly disabled, able to do fulltime work, 3 = mildly disabled, fully independent but not working, 4 = moderately disabled, almost independent for personal needs, 5 = severely disabled, walks only with help, 6 = chairbound. Operation notes were reviewed to ascertain the number and site of stereotaxic lesions, and the aids used to locate the target region, namely, cell recording or electrical stimulation or both. Postoperative complications were scored for severity (1 = mild, 2 = moderate, 3 = severe and disabling) and their progression noted in the postoperative epochs.

An overall assessment score of the efficacy of the operation was made and is given in the Tables shown in Results. The assessments are given as symbols, ranging from '−' (worst) to '+ + + +' (excellent). Intermediate grades of the symbols represent assessments as '=' unchanged, '+' slight improvement, '+ +' good improvement, and '+ + +' very good. These symbols of evaluation refer to the state of the patient's dystonia only and no attempt has been made to incorporate a measure of any disability resulting from operative side effects. Whether or not there were side effects which were of severity sufficient to be noted when the patient was seen after hospital discharge, is given in a separate column. The assessments of efficacy were made by the operating neurosurgeon. In most cases he was aware of the opinion of the referring neurologist. When possible his assesments were corroborated by the patient or a relative.

Also shown in the Tables are changes in disability score between the preoperative value and that rated when the patient was most recently seen or contacted.

The last two columns give the opinions of the patient and the neurosurgeon, respectively, of the total effect of surgery.

RESULTS

Table 1 summarizes the number of patients with each type of torsion dystonia. The definitions of three of the types of dystonia are those given by Marsden *et al.* (1976). Although the terms were originally used to describe idiopathic dystonias, they are essentially descriptive and may therefore also be used to describe symptomatic types.

TABLE 1. DISTRIBUTION OF TYPES OF DYSTONIA

Diagnosis	*No.*
Generalized dystonia	16
Segmental dystonia	13
Focal dystonia	14
Hemidystonia	12

Definition of Terms

The term *generalized dystonia* (GD) is used when the dystonic movements and postures spread from their site of appearance to involve all four limbs and axial structures.

The term *segmental dystonia* (SD) is used when the dystonic movements and postures spread to a limited extent, to involve at least two parts of the body, for example, an arm and the neck, or both arms and neck and trunk but sparing the legs.

Those in whom the dystonic movements and postures remain confined to the site of onset are said to have *focal dystonia* (FD) when a limb is affected, and *focal axial dystonia* when the neck alone is affected. The distinction between segmental and focal axial dystonia means that in this paper, those patients with spasmodic torticollis and some additional abnormality of an upper limb, have been classified as having segmental dystonia, whereas those with pure spasmodic torticollis, as focal axial dystonia.

The term *hemidystonia* is used here for those cases in whom the dystonic movements and postures are on one side of the body, implying contralateral localized brain pathology. This type of torsion dystonia was symptomatic of previous injury, vascular or inflammatory disturbance.

Generalized Dystonia

Table 2 gives details of 15 patients with GD. The clinical picture given here refers to the state of the patient at the time of operation. The case with involvement of 'mainly upper limbs, face and bulbar muscles' is included here rather than as a case of SD since he subsequently developed dystonia of the trunk and lower limbs.

Idiopathic generalized dystonia. Ten of the 16 cases with GD were thought to have been idiopathic. However, 3 patients amongst them had a somewhat atypical

TABLE 2. DETAILS OF PATIENTS WITH GENERALIZED DYSTONIA

Clinical picture	*No.*	*Pathogenesis*	*Age at onset (yrs)*	*Age at operation (yrs)*
Upper limbs, lower limbs, bulbar muscles, trunk	4	**2 idiopathic 2 postencephalitic	17, 15 2, 14	20, 26 17, 28
Mainly lower limbs, bulbar muscles, trunk	4	**3 idiopathic 1 perinatal injury	11, 14, 54 1	17, 20, 59 21
Upper and lower limbs and trunk	4	*2 idiopathic 1 postencephalitic 1 perinatal injury	2, 11 8 2	19, 13 10 32
Mainly upper limbs, face and bulbar muscles	1	Idiopathic	2	41
Lower limbs and neck	1	*Idiopathic	13	18
All limbs, not trunk	1	Taxoplasmosis gondii	10	11
Predominately hemidystonia	1	*Idiopathic	12	32

* Denotes generalized dystonia of 'adolescent' onset (Cooper, 1969) in one patient, ** in 2 patients.

history. In 2 of these the onset of symptoms was said to have been at about the age of 2 years, and it is thought that in cases with an age of onset at less than 4 years old, the condition is probably symptomatic of hitherto unrecognized perinatal injury. In one of our cases there was no history of the perinatal period available. In the other, the patient's mother described abnormal movements of her son's arms at the age of 1 year, and the disorder remained static until he was 39, when he rapidly became disabled by dystonia of the neck, face, bulbar muscles and upper limbs. Following surgery there was a brief remission in his condition, but the dystonia then spread to his trunk and legs as described in the preceding paragraph. The third case with an atypical history was a man, who, despite being 54 at the onset of his dystonic illness, started with symptoms in his legs, and who over the course of five years developed generalized involvement. Both onset in the lower limbs and a malignant course are not characteristic of late onset dystonia (Marsden and Harrison, 1974).

In the remaining 7 cases of idiopathic GD the onset of symptoms was between the ages of 11 and 17 years, and these could be considered to have had what Cooper termed the adolescent form of GD (Cooper, 1969). They are denoted by asterisks in Table 2. In only one case was there a positive family history in antecedents. One other of these cases had a cousin similarly afflicted. An Iranian boy with GD was the product of a first cousin marriage, and one of his younger brothers subsequently developed the same clinical picture. Another Iranian in this group with GD was also the offspring of a first cousin marriage. One of the 7 cases of idiopathic GD was Jewish.

Generalized dystonia from other causes. In 3 cases there was a history of the onset of dystonic symptoms at the time of a viral illness in previously healthy individuals. In no instance was the causative agent positively identified. In 2 cases symptoms were seen at 1 and 2 years of age, respectively, with a history of birth trauma and delay in developmental milestones. In one case the history was of onset of symptoms one year earlier in a previously healthy girl from Oman. A brain biopsy taken at the time of stage I of stereotaxic surgery showed changes of chronic leptomeningitis, thought to be due to Toxoplasma gondii.

Segmental Dystonia

Table 3 gives details of the 13 patients with SD. In only one case was there a positive family history and that patient's sister had a similar disorder of gait. All but one case were thought to be idiopathic in nature, and details of this exception are given below.

Eight cases had spasmodic torticollis as the major symptom, but additional symptoms affecting an upper limb, either tremor or dystonia, prevented these cases being classified as FD. However, the results of surgery in these 8 cases are discussed along with those of isolated torticollis (Table 8).

The one case with nonidiopathic SD had tonic torticollis with deviation of the neck to the side of the dystonic arm. The pathogenesis in this instance was thought

TABLE 3. DETAILS OF PATIENTS WITH SEGMENTAL DYSTONIA

Clinical picture	*No.*	*Pathogenesis*	*Age at onset (yrs)*	*Age at operation (yrs)*
Spasmodic torticollis UL + tremor	4	Idiopathic	45–51	49–56
Spasmodic torticollis UL + dystonia	4	Idiopathic	20–66	37–67
Tonic torticollis UL + dystonia	1	Spastic UL from perinatal injury	20	28
Dystonia both UL + spasmodic torticollis	1	Idiopathic	48	58
Dystonia both UL	1	Idiopathic	12	22
Both lower limbs	1	Idiopathic, familial	10	23
Neck and trunk	1	Idiopathic	22	26

UL = upper limb.

to be due to a perinatal injury, since the arm had been spastic since birth until the onset of dystonic posturing at the age of 20 years.

Focal Axial and Focal Limb Dystonia

Table 4 gives details of the 14 patients with FD. Eleven had idiopathic spasmodic torticollis with a mean age of 50 years. One patient had idiopathic retrocollis, another had dystonic writer's cramp and one case had severe dystonia of one arm only. Like the two cases of GD already mentioned, this last patient was the product of a first cousin Iranian marriage.

TABLE 4. DETAILS OF PATIENTS WITH FOCAL AXIAL OR FOCAL LIMB DYSTONIA

Clinical picture	*No.*	*Pathogenesis*	*Age at onset (yrs)*	*Age at operation (yrs)*
Isolated spasmodic torticollis	11	Idiopathic	23–70	25–71
Retrocollis	1	Idiopathic	54	58
Writer's cramp	1	Idiopathic	23	39
Upper limb	1	Idiopathic	22	25

Hemidystonia

Table 5 gives details of the 12 patients with hemidystonia. In 10, the arm was chiefly affected although there was evidence of involvement elsewhere in a unilateral distribution. In one case there was involvement of the arm only, but the abnormality developed following the recovery from a complete hemiparesis of unknown cause.

TABLE 5. DETAILS OF PATIENTS WITH HEMIDYSTONIA

Clinical picture	*No.*	*Pathogenesis*	*Age at onset (yrs)*	*Age at operation (yrs)*
Arm, neck and face	1	Post infantile hemiplegia	2	21
Principally arm but leg involved to lesser extent	7	3 postencephalitic	7, 10, 25	9, 14, 26
		2 perinatal injury	0, 0	16, 20
		1 ?tuberculoma	6	22
		1 post hemiplegia	11	19
Mainly arm but face and leg also	2	1 postencephalitic	10	20
		1 post head injury	8	24
Arm only	1	Post hemiplegia	25	27
Leg only	1	Post head injury	19	22

Likewise, the instance of torsion dystonia affecting only the leg followed recovery from a full hemiparesis which occurred as a result of a head injury.

Results of Thalamotomy for Generalized Dystonia

Table 6 summarizes the outcome of the results of stereotaxic surgery in patients with GD. The patients are grouped according to their degree of disability preoperatively.

There was no consistent relationship between the patients' duration of illness (Table 2) and their preoperative disability, except that the 4 who were bedridden and who died within a year of operation all had a short history of less than five years' duration.

The number of stereotaxic lesions made on each side are given in the second column of Table 6; 'p' indicates an additional lesion in the pulvinar. The four columns containing symbols summarize the result of stereotaxic surgery, when assessed at the time intervals shown. These assessments, shown at the bottom of the Table, give grades of change, from worst to excellent. As explained in Methods, these assessment scores were given by the operating neurosurgeon, aided by reference to the notes and discussion with the referring neurologist. When possible the assessments were corroborated by the patient or a relative.

The change in disability score was derived by subtracting the score rated preoperatively from that rated at the most recent assessment. The scoring system is detailed in Methods. A negative score indicates an improvement.

The last two columns give the patient's or a relative of the patient and the neurosurgeon's overall assessment of the efficacy of surgery. Statements within inverted commas indicate that the comment has been transcribed verbatim from a letter or discussion.

Fourteen patients were followed for a period of more than one year. Four had died by then as a consequence of their dystonia, 2 had shown a favourable response to surgery initially, but then relapsed and were in a worse condition than preoperatively, and 2 remained unaltered by surgery. Only 6 showed any degree of improvement at one year.

Of these cases, one had idiopathic GD in a predominately unilateral distribution, and following unilateral lesions improved sufficiently to return to work as a nurse.

The second patient who showed an improvement had had abnormal movements of his arm since the age of 1 year. The disorder remained static until he was 39, when he rapidly became disabled by dystonia of the neck, face, bulbar muscles and upper limbs. Following bilateral thalamotomies the dystonia was much improved for approximately four years. After that time the condition spread to affect the trunk and legs and he died fifteen years after operation.

For 3 cases, very painful leg spasms were abolished by bilateral thalamotomies. One patient suffered a deterioration six years later and he died eight years after surgery with dystonic spasms affecting the upper and lower limbs. Another case remains spasm free six years after surgery. In the third case the dystonic movements persist but they are no longer painful.

The final case showed a very striking improvement. Following encephalitis two years earlier this girl had developed GD with involvement of all limbs, trunk and bulbar muscles, so that preoperatively she was barely able to walk. Four days after completion of bilateral thalamotomies she developed gross, generalized continuous movements. For three weeks she was pyrexial with a temperature reaching 105° C, which was thought to be due to hyperkinesis since thorough attempts to isolate an infective organism failed. Gradually over the course of the ensuing four weeks the abnormal movements abated, her mobility improved, and a year later she was able to run and was doing well at school.

Table 6 shows that pulvinar lesions were made in 3 patients. From this limited experience, we concluded that they were not effective in the treatment of GD.

Results in Idiopathic Typical Generalized Dystonia of Juvenile Onset

In Table 6 the 7 patients with the 'adolescent form' of GD are again marked by asterisks. As may be seen, 3 were dead within a year of surgery. One of these cases died suddenly on the second postoperative day with unexplained hyperthermia following unilateral thalamic lesions which had been made under general anaesthetic. This was the only case when general anaesthesia had been given for stage II of the procedure. The other 2 deaths occurred in severely disabled patients who had had the full number of bilateral lesions. The 3 cases marked by asterisks who improved following surgery are 3 of the cases already described in preceding paragraphs. The sixth and seventh cases GD of juvenile onset had only shortlived remissions from dystonia.

Results of Thalamotomy in Hemidystonia

Table 7 shows the result of surgery for hemidystonia. Although abnormal movements were not abolished totally, all the patients had a worthwhile functional improvement to a greater or lesser extent, as shown.

TABLE 6. SUMMARY OF THE OUTCOME OF STEREOTAXIC SURGERY IN GENERALIZED DYSTONIA

Disability pre-op. (*No. of patients*)	*No. of lesions* *R*	*L*	*Before discharge*	*Outcome* *< 1 yr*	*> 1 yr*	*> 3 yrs*	*Change of disability grade*	*Operative S/Es*	*Patient's opinion*	*Neurosurgeon's opinion*
Fully independent (4)	*3 + p	3 + p	+	—	—	—	+ 2	Yes	Thought to regret surgery	No long-term benefit but side effects persist
	3	3 + p	+ +	+ +	+	Died[1]		No		Relieved spasms for 4 years
	*1	3	+ + +	+	=	—	+ 1	Yes	'Deterioration 9 months later was alarming, rapid'	Initial improvement not sustained
	2	2	=	=	=	N/K	0	Yes	Wanted more surgery done	Failure
Moderately disabled e.g. walking only with help (4)	*0	3	+	+	+ +	+ +	− 2	Yes	Patient: 'did a lot of good'. Husband: 'almost a miracle'	Worthwhile
	2	2	+	=	—	—	+ 1	Yes	Mother: 'first side was good, second side set him back'	General condition worse after second side
	1	1	=	N/K	N/K	N/K	0	No	N/K	Advanced case who showed no improvement
	2	2	+	+ +	+ + +	+ + + +	− 4	Yes	Enjoying full school life	Very worthwhile
Chairbound or bedridden (8)	1	3	+	+	+ +	Died[2]		No	N/K	Relieved of painful leg spasms for 6 years
	*3	1	+ +	+ +	+ +	+ +	− 1	Yes	Sister: 'she's glad there's no more pain'	Worthwhile because of pain relief
	1	1	+	+	=	=	0	Yes	Mother: 'she's thankful despite effect on voice'	Worthwhile because of pain relief
	1	1	+	N/K	N/K	N/K	0	No	N/K	Lost to long-term follow-up
	*0	3	Died	Dead	Dead	Dead		Yes		Unexplained hyperthermia followed by death
	*3	3	—	Died	Dead	Dead		Yes		Totally incapacitated and in pain
	0	3	Died	Dead	Dead	Dead		Yes		Operation undertaken on strength of Cooper's claims (Cooper, 1969)
	*3 + p	3 + p	Died	Dead	Dead	Dead				

* Denotes GD of 'adolescent' onset (Cooper, 1969). [1] Relapsed 4 years after operation and 11 years later, died. [2] Relapsed 6 years after operation and 8 years later, died. p = pulvinar. − worse. = unchanged. + slight improvement. + + good improvement. + + + very good. + + + + excellent. N/K not known. S/Es = side effects.

TABLE 7. OUTCOME OF THALAMOTOMY IN PATIENTS WITH HEMIDYSTONIA

Disability pre-op. (*No. of patients*)	*No. of lesions* *R*	*L*	*Before discharge*	*Outcome* *< 1 yr*	*> 1 yr*	*> 3 yrs*	*Change of disability grade*	*Operative S/Es*	*Patient's opinion*	*Neurosurgeon's opinion*
Socially disabled (2)	3	0	+	+ +	+ +	+ +	− 1	Yes	Very pleased	Greatly increased use of hand
	0	3	+ + +	+ + +			− 1	No	'Really pleased, using my hand a lot'	Recently done, excellent initial response
Mildly disabled (6)	2	0	+ +	N/K	N/K	N/K	− 2	No	N/K	Lost to follow-up (f.u.)
	0	2	+ + + +	N/K	N/K	N/K	− 2	No	N/K	Good immediate response, lost to f.u.
	3	0	+ + +	+	+	+	0	No	Pleased, lost aching discomfort	Worthwhile
	0	3	+ + +	+ + + +	+ + +	+ + +	− 1	No	Very pleased	Worthwhile
	0	2	+ + + +	+ + + +	N/K	N/K	− 3	No	Family and patient very pleased	Very worthwhile
	0	1	+ + + +	N/K	N/K	N/K	− 3	No	Very pleased	Very worthwhile
	0	2	+ + +	+ + + +			− 1	No	Very pleased	Very worthwhile
Moderately disabled, almost independent (3)	0	2	+ +	N/K	N/K	N/K	− 1	No	N/K	Worthwhile, no long-term f.u.
	3	0	+ +	N/K	N/K	N/K	− 1	No	N/K	Worthwhile, no long-term f.u.
	1	0	+ + + +	N/K	N/K	N/K	− 4	No	N/K	Remarkable, no long-term f.u.

f.u. = follow-up. For explanation of other symbols, *see* Table 6.

Unfortunately, follow-up is incomplete in these patients as 7 of the 11 came from the Middle East. However, in those for whom follow-up is available, the beneficial effect of the operation persisted. As can be seen from Table 5 the pathogenesis in these cases was nonprogressive, which may be a factor contributing to the sustained improvement.

Although positive follow-up was not available in so many of the cases, it is highly likely that the patients would have requested rereferral in the event of a deterioration, as was done by 2 patients with GD from the Middle East who did not improve.

Results of Thalamotomy for Spasmodic Torticollis

The results of stereotaxic thalamotomy for spasmodic torticollis is a manifestation of focal axial dystonia (Table 4) and SD (Table 3) are shown in Table 8. In assessing the success of surgery for spasmodic torticollis it has been pointed out that in this condition the patients' opinion of their condition may differ from that of the objective assessor (Hamby and Schiffer, 1969; Meares, 1971). To simplify the presentation of the results, this problem has been avoided and the evaluations given in Table 8 show score assessments based only on observations of the authors, advised where possible by the referring physicians. In fact there were only 2 cases where it was known that the patients' opinion differed from that of an objective assessor. In addition, the results represented in symbols in Table 8 do not include any evaluation of disabilities which resulted from operative complications. All scores refer to improvement in spasmodic torticollis, with the exceptions of the 2 cases with segmental dystonia in whom tremor was the main symptom to be improved. These have been marked accordingly.

Of the 16 cases who underwent bilateral thalamotomies, 10 (62 per cent) obtained good relief from their torticollis. There were 3 patients who were initially improved but who then relapsed. There were 3 in whom no beneficial effect was produced, and one of these subsequently died. This gives a failure rate of 38 per cent. However, there was also a high incidence of persisting dysarthria in this group. This is detailed in the section on complications (*see below*).

Amongst the group with spasmodic torticollis there were 6 cases who had only unilateral thalamotomies. Bilateral lesions were not attempted because of operative complications. Of the 6 cases, 3 were not improved but 2 of the patients, who were classified as having SD, did obtain a good result as both had relief from symptoms of disabling tremor in the contralateral arm. The sixth case was found on examination of the CSF to have neurosyphilis, and symptomatic improvement in his torticollis coincided both with a unilateral thalamotomy and penicillin treatment.

Results of Thalamotomy in Other Dystonias

There were 5 further patients whose response to surgery does not appear in a table. There were 3 patients with SD (Table 3) in whom spasmodic torticollis was not the predominant complaint. The patient with a gait disorder from involvement of both

TABLE 8. RESULTS OF STEREOTAXIC SURGERY FOR DIFFERENT TYPES OF TORTICOLLIS

Type of torticollis	*No. of lesions*		*Before discharge*	*Outcome*			*Change of disability grade*	*Operative S/Es*	*Patient's opinion*	*Neurosurgeon's opinion*
	R	*L*		*< 1 yr*	*> 1 yr*	*> 3 yrs*				
Spasmodic torticollis	3	4	+ + + +	+ + + +	+ + + +	+ + + +	−2	No	N/K	Excellent result
	3	2	+ + + +	+ + + +	+ + + +	N/K	−1	Yes	N/K	Very well worthwhile, despite dysarthria
	3	1	+ + +	+ + +	+ + +	+ + +	−2	Yes	Very pleased	„ „ „ „ „
	2	3	+ + +	+ + +	+ + +	N/K	−2	Yes	S/Es were 'small price to pay'	„ „ „ „ „
	3	1	+	+ +	+ + +	+ + +	−3	Yes	S/Es accepted happily	„ „ „ „ „
	3	3	+ + +	+ + +	+ + +	N/K	−2	Yes	N/K	Worthwhile early improvement
	1	3	+	+ +	=	N/K	+2	Yes	N/K	Worthwhile
	3	2	+	+ +	—	—	0	Yes	N/K	Not worthwhile
	3	3	+ +	=	—	—	+3	Yes	Committed suicide	Failure
	0	2	=	+	+	N/K	−1	Yes	Very depressed, not coping	Not worthwhile because of hemiplegia
	1	0	—	—	=	=	0	Yes	N/K	Not worthwhile
Retrocollis	3	3	—	Died			0	Yes		
Spasmodic torticollis and tremor of an upper limb	2	3	+ + +	+ + +	+ + + +	N/K	−1	Yes	N/K	Worthwhile
	2	2	+ + +	+ + + +	+ + + +	N/K	−2	Yes	'People were astonished'	Very worthwhile
	0	3	+ + + (Tremor)	+ + +	+ + +	N/K	−2	Yes	Pleased	Worthwhile
	0	1	+ + + (Tremor)	+ + +	+ +	N/K	−1	Yes	N/K	Worthwhile
Spasmodic torticollis and dystonic upper limb	1	2	+ + +	+ + +	+ + +	N/K	−1	Yes	'Still got terrible tensions'	Not happy although neck movements better
	2	3	+ + +	+ + +	+ + +	+ +	−1	Yes	'Helped immensely'	Worthwhile, despite dysarthria
	1	1	=	=	=	=	0	Yes	N/K	Unsuccessful
	1	0	=	=	=	N/K	0	Yes	N/K	Unsuccessful
Tonic torticollis and spastic upper limb	2	3	=	=	=	=	+1	Yes	N/K	Unsuccessful
Dystonia of both upper limbs and spasmodic torticollis	0	3	+	=	=	=	0	Yes	N/K	Unsuccessful

For explanation of symbols, *see* Table 6.

lower limbs had three lesions bilaterally, but with no improvement. By contrast, the patient with involvement of the trunk and neck had an excellent response, and from walking only with difficulty preoperatively, is now, seven years later, fully mobile and working again as a medical practitioner. The case with involvement of both upper limbs obtained greatly improved use in her hands following thalamotomy.

The last 2 cases in the series had focal limb dystonia. One is a patient with dystonic writer's cramp who, after an initial improvement, relapsed six weeks later back to his preoperative state. The other case had isolated dystonia of his right arm and obtained an excellent response to thalamotomy, which has been maintained for the last six months.

Complications

The most commonly seen neurological complications following stereotaxic surgery were hemiparesis and dysarthria. A hemiparesis usually resolved, whereas improvement in dysarthria was less good.

Hemiparesis. Following thalamotomy, it was noticed that a proportion of the patients scuffed their foot on walking, although there was no detectable weakness of the limb when they were examined supine. This mild abnormality had usually resolved within two weeks.

There was one case who had developed dystonic symptoms on recovering from an infantile hemiplegia, and following thalamotomy had a hemiparesis which took several months to resolve.

Of the other 54 patients there were 16 who had a hemiparesis of some degree at the time of discharge postoperatively. At one year only 12 of the 16 cases could be traced; 7 had then completely recovered, leaving 5 with a lessened, but persisting, mild hemiparesis. Amongst these 5 cases was a patient who was aged 71 years at the time of surgery, and another aged 60 years, who was hypertensive.

The complication of a hemiparesis was as common in those who had had unilateral lesions as in those with bilateral lesions. The incidence could not positively be related to whether or not evoked responses were recorded at the time of thalamotomy. In this series the incidence of a hemiparesis known to have lasted for more than one year is 16 per cent. This figure is calculated from the incidence amongst those in whom follow-up information is available for over a year postoperatively, and excludes those who died.

Dysarthria. Preoperatively, 10 of the 55 patients had dystonic dysarthria of a varying degree. Postoperatively 9 of this group suffered a deterioration in speech. All but one case had had bilateral lesions. There was, therefore, only one case with GD with bulbar muscle involvement whose dysarthria was not made worse by thalamotomy.

Only one of the patients with a postoperative exacerbation was recorded to have shown much improvement over the course of the following year, and one case showed a marked progression of dysarthria.

Of the 45 cases with no speech difficulty preoperatively, 20 had some degree of dysarthria postoperatively. All but one of these patients had had bilateral thalamic lesions.

At an interval of more than one year, 3 of the 20 were not available for follow-up and one had died. Dysarthria had completely resolved in 2 cases, leaving 14 patients known to have persistent dysarthria. In 8 patients the dysarthria was mild and, although noticeable, did not interfere with the comprehensibility of speech. In the other 6 the dysarthria was a considerable impediment. The known incidence of dysarthria amongst survivors and those not lost to follow-up is 1 in 9 (11 per cent) for unilateral lesions and 13 in 23 (56 per cent) for bilateral lesions.

Pseudobulbar palsy. Seven of the patients who had had bulbar muscle dystonia and were dysarthic developed difficulty swallowing as well as with speech following thalamotomy. All 7 cases had had bilateral lesions.

Three of these patients died within six months of operation. In the other 4, difficulty with swallowing improved so that it was no longer a complaint when the patients were seen at an interval of more than one year.

There were, in addition, 8 patients who had had no bulbar muscle difficulties preoperatively but who were dysarthric postoperatively, and also had difficulty swallowing. All had had bilateral lesions. One of these patients died within two months of surgery. In the others the difficulty with swallowing improved and at an interval of more than one year, none had any complaints related to eating or swallowing, although 7 had persistent dysarthria, as mentioned above.

Ataxia. Twelve of the 55 cases had ataxia of either an arm or leg postoperatively. Follow-up information is only available in 8 of the cases. In these, ataxia is known to have resolved completely in 3 and lessened in severity in 2, but remained the same in 3.

Other side effects. Paraesthesiae. Five patients had persistent paraesthesiae postoperatively in the hand and face, but this complaint persisted for more than one year only in one.

Epilepsy. One patient who had had hemidystonia following an infantile hemiplegia developed grand mal epilepsy within a year of stereotaxic thalamotomy.

Personality change. There were 3 cases in whom relatives reported a change in personality postoperatively. One patient was said to have become less inhibited and in the second the changes were not specified but said to have contributed to divorce. The third patient was considered by her husband to have become 'more muddled'.

Conclusion on Complications

The incidence of hemiplegia is similar in that group who had unilateral lesions (1 in 9) to those in the group who had bilateral lesions (3 in 23). However, the incidence of dysarthria in those who did not have bulbar dystonia preoperatively is much higher in those with bilateral lesions (13 in 23) compared with the incidence in those with unilateral lesions (1 in 9). Nine out of 10 patients with preoperative bulbar dystonia suffered a deterioration in speaking and all but one had had bilateral lesions.

Of the 55 cases who had stereotaxic surgery there were 10 who had considerable postoperative complications. All but one of these cases had had bilateral lesions. Five of the 10 cases were in a desperate plight preoperatively, being severely crippled by dystonic movements and either chairbound or bedridden. These 5 cases had little or no benefit from surgery and their neurological status was worse postoperatively and continued to deteriorate until they died.

Of the other cases there were 5 who developed considerable postoperative complications, 2 unfortunately had a combination of hemiparesis, difficulty with swallowing and dysarthria. Two of the other 5 cases with premorbid personality disorders reacted badly to new neurological disturbances postoperatively, although spasmodic torticollis had been abolished in one instance. The fifth case with considerable postoperative difficulties suffered a very severe deterioration of GD from which it was thought she would die. However, four weeks after surgery she started to improve and eventually made an excellent recovery, as already described.

In general, as expected, those for whom the original complaint was abolished, or much improved, tolerated operative side effects much better than those for whom there was little benefit. Two patients with dysarthria but in whom spasmodic torticollis had been abolished, said that difficulty with speech was a 'small price to pay for cure from their torticollis'.

DISCUSSION

History

Stereotaxic lesions were developed primarily for the treatment of parkinsonian tremor and rigidity. Initially the target site was in the globus pallidus (Meyers, 1942), but lesions in the lateral thalamic nucleus were then found to give better results (Cooper, 1954; Hassler, 1956).

When operating on patients with Parkinson's disease, Cooper noticed that not only tremor but also any coexistent dystonic symptoms were reversed by stereotaxic thalamotomy (Cooper, 1969). Cooper was working at St Barnabas Hospital in New York at the time, where there is a high incidence of generalized idiopathic torsion dystonia (dystonia musculorum deformans, DMD) amongst the Ashkenazim (Eldridge, 1970). In Cooper's own words (Cooper, 1969), there was then an 'abysmal view of the therapeutic possibilities' for treatment of DMD, and so he initiated stereotaxic thalamotomy for the treatment of the condition.

Target Area

Cooper recommended the target sites Vim, CeM and Vce/i for surgery in dystonia (Cooper, 1969), giving a comma shaped lesion, supplemented where necessary by a pulvinar lesion. Why ablation of these target areas should sometimes prove effective remains unknown. Vim in the human is known to receive proprioceptive and kinaesthetic input and possibly vestibular connections (Ohye, 1978). CeM receives efferent fibres from the cerebellar nuclei *via* the brachium conjunctivum. Efferent fibres from CeM pass to the striatum where they synapse with fibres in a reverberating nigrostriatal circuit. Vce is the somatosensory relay nucleus for the limbs and trunk, Vci the sensory relay nucleus for the face (Hassler *et al.*, 1979).

A little more is known about the rationale for the target sites in surgery for tremor and for that reason a short discussion is pertinent here. Although in the past other areas of the thalamus were sought (Hassler *et al.*, 1979), it is now generally agreed that the target site is that part of the lateral ventral thalamus in which neuronal activity is time-locked to peripheral tremor (Narabayashi, 1982).

Albe-Fessard, who first demonstrated the rhythmic thalamic activity in parkinsonian patients (Albe-Fessard *et al.*, 1966) proposed that the activity that was precisely in phase with peripheral tremor was itself part of a tremorogenic mechanism. Jasper and Bertrand (1966) suggested that the thalamic rhythms time-locked to the tremor are part of a 'self-sustained tremorogenic mechanism in the thalamus and motor cortex, which serve as a pacemaker for tremor'. Narabayashi and Ohye (1978), however, consider that bursts synchronous with tremor are a reflection of peripheral kinaesthetic effects.

Nevertheless, it is by a discrete lesion destroying the tremor-locked firing neurons in Vim, that tremor may be immediately abolished without side effects (Narabayashi 1982). Vim is thought to project to the motor cortex (Ohye, 1978), and possibly the interruption of this pathologically synchronous input to the motor cortex abolishes a tremorogenic effect which is mediated *via* the corticospinal tract on the anterior horn cells. In dystonia, however, it is not known whether dystonic movements are mediated by motor cortex or brainstem tracts or both.

The response of GD to stereotaxic thalamotomy differs from that seen with tremor in that the improvement, if any, is not always immediate, but gradual, over the course of the ensuing days or weeks. This phenomenon was described by Cooper (1969) but was also noted in four patients who responded favourably in this series. The mechanism of this effect is therefore even more difficult to comprehend than that proposed for the effect of thalamotomy in tremor.

Results of Surgery for Dystonia

Between 1953 and 1976 Cooper operated on 227 cases with GD and claimed a 69.7 per cent incidence of lasting moderate or marked improvement (Cooper, 1976). We have found, much the same as have other authors of smaller series (Markham and Rand, 1961; Riechert, 1962; Marsden, 1981), that our results for surgery in GD are not as good as those claimed by Cooper.

However, of the 16 patients in this study with GD, only 10 were thought to have been idiopathic. Only 7 of those (marked by asterisks in Tables 2 and 6), had typical 'adolescent' generalized dystonia, and only one was ethnically Jewish. Cooper states that in his experience those cases which respond best are the young Ashkenazi children with a positive family history (Cooper, 1976). Of the 4 cases with a good response in our series, 3 were thought to have had typical GD of adolescent onset and one of those had a positive family history. This difference in case mix may well explain the poorer results described here for patients with GD, as compared with those given by Cooper.

Although the target area was the same (that is, CeM, Vim and Vce/i) in our series as that recommended by Cooper, we made a smaller lesion, an ovoid measuring 6 mm × 3.5 mm at its maximum diameter (Watkins, 1965), compared with his spherical lesions with a diameter of between 7 and 10 mm (Cooper, 1976). In our experience the limiting factor for making bilateral multiple lesions was the onset of operative side effects, in particular, pseudobulbar palsy. The proximity of the corticobulbar tract to Vim, the target site, has been stressed by Bertrand (1981). The comparatively high incidence of pseudobulbar palsy in this series can be contrasted with the 18 per cent incidence of the complication in Cooper's series, despite the procedure here being carried out in stages, usually with cell recording and almost always in an awake patient. Our patients did not have the same 'resilience' that Cooper claimed for his (Cooper, 1969).

Despite a smaller volume lesion being used in this series, the method was highly successful in the treatment of hemidystonia (*see* Table 8), and the response rate was also higher in the group with FD than in those with GD. This would tend to indicate a peculiar resistance to improvement in GD. Nevertheless, in light of the fact that 5 patients with GD obtained a substantial relief from their symptoms, stereotaxic surgery must continue to be considered in GD in the absence of any other effective treatment.

Results for Spasmodic Torticollis and Retrocollis

In 1977 Cooper published the results of bilateral thalamotomies in 160 patients with spasmodic torticollis operated on between 1957–1977 (Cooper, 1977). Sixty per cent of his patients obtained 'satisfactory alleviation' of symptoms but 20 per cent developed dysphonia. The figures for the success rate of the operation are very similar for the present series (i.e. 62 per cent good result) with a comparable relapse rate (3/16 in ours) and nonresponse rate (3/16). Cooper's incidence of dysphonia was 20 per cent and ours 56 per cent.

Although detailed discussion of postoperative dysarthria in these patients has not appeared in the literature, it is believed that it has been a major factor in deciding whether to recommend thalamotomy (Marsden and Fahn, 1982*b*). When medical treatment fails there is often a request for surgical intervention. What should be the advice?

The offer and choice of surgical treatment in these patients is difficult. The simpler surgical procedure is anterior cervical rhizotomy with division of the sternomastoid branch of the spinal accessory nerve. Yet the failure rate in this operation is about the same as for bilateral thalamotomy and this operation also has its postoperative complications. These include oedema of the spinal cord due to ischaemia following the cutting of anterior roots which contain some small blood vessels feeding the spinal cord; postoperative epidural haematoma leading to cord compression; difficulty with swallowing even for some considerable time after operation due to the fact that the patient cannot easily extend the neck as a part of the act of swallowing; weakness of the shoulders; and often severe pain in the region of the shoulders for a number of weeks afterwards. The dystonic movements may also return.

As there is a small spontaneous remission rate (Meares, 1971) no operation should be considered for several years. Appearance of cervical myelopathy, severe nuchal pain, or increasing disability leading to jeopardizing the ability to earn a livelihood have been the usual indications.

Our Results for Hemidystonia

There was a uniformly good response to thalamotomy in those with hemidystonia, and since the operation was unilateral, the incidence of untoward side effects was very low.

From Table 5, showing the presumed pathogenesis of each case, it is clear that there were diverse pathologies. In 2 of these cases the site of the pathology was identified on the brain scan (one case was described in some detail by Andrew *et al.*, 1982*a*) and in neither of these cases was the pathology at the same site. It is highly probable that there were many differently sited lesions amongst this group of patients. This makes the uniformly good response remarkable in terms of a pathophysiological explanation.

Less has been written on the response of hemidystonia than that of hemiballismus and hemichorea to stereotaxic thalamotomy. Carpenter (Carpenter *et al.*, 1950) showed that in the monkey, destruction of 20 per cent of the subthalamic nucleus could produce hyperkinesia, choreiform and some ballistic movements of the contralateral limbs, and a lesion of the ipsilateral pallidum or ventrolateral nucleus would abolish the movements. Grossman and Kelly (1976) suggested that the mechanism of the therapeutic lesion is to interrupt the circuit by which outflow from the pallidum, disordered by the loss of the subthalamic nucleus function, enters the motor cortex *via* the thalamus. Clearly this explanation does not hold for all cases of hemiballismus, since in a number of cases the primary pathology has been shown to be at sites other than the subthalamic nucleus (Gioino *et al.*, 1966).

The predominant clinical picture in the cases included here in the group termed hemidystonia was of dystonic muscle contractions in the limbs, but in many of them there was some superimposed violent movement, as was the case in the group of patients we have recently described with posttraumatic tremor (Andrew *et al.*, 1982*b*). These more rapid, distal movements responded particularly favourably to stereotaxic surgery.

This group of patients who develop dystonia following unilateral structural damage has therefore been identified as being highly suitable for stereotaxic thalamotomy: the response rate is high and the incidence of operative complications low.

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THE CORRELATION BETWEEN TREMOR CHARACTERISTICS AND THE PREDICTED VOLUME OF EFFECTIVE LESIONS IN STEREOTAXIC NUCLEUS VENTRALIS INTERMEDIUS THALAMOTOMY

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SUMMARY

In 51 cases (6 cases with bilateral operations) with various kinds of tremor, stereotaxic ventralis intermedius (Vim) thalamotomies were performed using Leksell's apparatus and the results of operation evaluated. Several characteristics of the tremor, including clinical features and EMG, were correlated with the assumed location and volume of the coagulative lesion. In 54 of the 57 operations, the thalamic Vim nucleus was identified physiologically and a therapeutic lesion placed at a site that included the Vim neurons. In all these cases, except one in which the lesion was estimated to be too small, tremor was immediately abolished by a relatively small lesion. The estimated volume of the lesion was about 40 to 200 mm^3 and the effect persisted over a long follow-up period (maximum ten years). The size of the lesion that was necessary apparently depended on several features of the tremor. A larger lesion was required in cases of movement type tremor, tremor with a low rate (less than 4 Hz), tremor of high amplitude (more than 600 μV), and tremor involving proximal muscles or with a wide distribution. Tremor following a cerebrovascular lesion and post-traumatic tremor were characterized by coarse oscillation (high amplitude and low frequency) involving proximal muscles. A relatively larger coagulative lesion was therefore necessary to relieve this type of tremor. In contrast, parkinsonian and essential tremor were usually of low amplitude and distal in distribution. For the relief of such tremor, the lesion could be very small: if aided by electrophysiological methods to identify Vim neurons, the minimal effective volume of the lesion was estimated as about 40 mm^3 and restricted to the Vim nucleus. Based on these results, the importance of the Vim nucleus in tremor mechanisms is discussed.

INTRODUCTION

Although L-DOPA therapy is the first choice for the treatment of parkinsonian tremor, physiologically controlled stereotaxic thalamotomy (G. Bertrand *et al.*, 1969; C. Bertrand *et al.*, 1973; Guiot *et al.*, 1973; Riechert, 1973; Ohye, Fukamachi *et al.*, 1977) is still employed in the treatment of tremor because of its reliable therapeutic effectiveness. Since 1972 we have performed stereotaxic operations, notably Vim (nucleus ventralis intermedius) thalamotomy, for the treatment of tremor using microelectrodes (Albe-Fessard *et al.*, 1963; Jasper and Bertrand, 1964; G. Bertrand *et al.*, 1967; Fukamachi *et al.*, 1977; Nakajima *et al.*, 1978), an operation for producing a small localized coagulative lesion within the physiologically identified Vim nucleus of the thalamus (Ohye, Maeda *et al.*, 1977; Narabayashi and Ohye, 1978; Ohye, 1978; Ohye and Narabayashi, 1979; Ohye, Hirai *et al.*, 1982). In the present study, the results of Vim thalamotomy in parkinsonian and other types of tremor were analysed, including idiopathic or essential tremor, post-traumatic tremor (PTT), tremor following cerebrovascular lesions (post-CVD tremor) and writer's cramp. The term 'writer's cramp' is used here for cases with primary writing tremor (Ohye, Miyazaki *et al.*, 1982). The relationships between the location and predicted volume of the coagulative lesion were deduced from physiological and radiological data. Several aspects of tremor have been investigated and some questions relevant to the treatment of tremor are discussed.

MATERIAL AND METHODS

Patients

From a series of cases of stereotaxic operations performed in the Department of Neurosurgery, Gunma University Hospital, during a seven-year period from July 1972 to August 1978, 51 cases operated upon for the relief of tremor were studied. The underlying pathology in these 51 cases is given in Table 1. Twenty cases of L-DOPA resistant Parkinson's disease (9 males and 11 females, age range 43 to 70 yrs) all had prominent tremor with only slight rigidity. Tremor of unknown aetiology with no other attendant neurological manifestations were grouped into the essential or idiopathic variety (7 males and 8 females, aged 21 to 66 yrs). In 3 cases of post-CVD tremor (2 males and 1 female, age range 45 to 58 yrs), coarse tremor occurred, predominantly on the paralysed side, during the course of recovery from paralysis due to a cerebrovascular lesion. In 5 cases of post-traumatic tremor (4 males and 1 female, age range 16 to 50 yrs), the tremor was persistent and had its onset in the recovery stage after severe head injury accompanied by impairment of consciousness. In addition, 2 cases of writer's

TABLE 1 NO. OF OPERATED CASES

Classification of tremor	*No. of cases*	*No. of operations*
Parkinson's disease (tremor type)	20	26
Tremor	31	37
Essential tremor (aetiology unknown)	15	17
Post-CVD tremor	3	5
Post-traumatic tremor	5	5
Writer's cramp	2	3
Tremor combined with		
Tumour	2	2
OPCA	1	1
Cerebral palsy	1	2
Intention myoclonus	2	2
Total	51	63

OPCA = olivopontocerebellar atrophy.

cramp (2 males, 36 and 47 yrs) and 6 cases of tremor associated with various other diseases were also included in this series. Of these 6 latter cases, 2 were of tremor accompanying intracranial tumours, with the onset occurring after operation for an acoustic neurinoma in one (female, 66 yrs) and after irradiation of a thalamic tumour in the other (male, 66 yrs). Two cases of tremor concurrent with intention myoclonus were due to methyl bromide poisoning (female, 27 yrs) and anoxia caused by asthmatic attacks (female, 60 yrs), respectively. In the remaining 2 cases, the tremor was a symptom of olivopontocerebellar atrophy (OPCA) in one (male, 43 yrs) and of cerebral palsy (male, 17 yrs) in the other.

Classification of Tremor Characteristics

In each case, tremor was analysed in terms of its clinical and electromyographic (EMG) features and classified and symbolized in the undermentioned manner. Electromyographic recordings were obtained from as wide an area of the superficial musculature as possible, including not only the limbs but also proximal muscles of the trunk (deltoid, pectoralis major, latissimus dorsi, etc.) and neck muscles. For this purpose, a pair of plate electrodes were pasted on the surface of the corresponding muscle belly about 2 cm apart and connected to an ink-writing multipurpose EMG machine (Nihonkohden, ME-175D, time constant 0.05 s with a standard amplification of 200 μV/7 mm). The EMGs of at least a pair of antagonist muscles (e.g. biceps and triceps muscle of the upper arm) were recorded simultaneously (maximum: 12 channels). (1) According to the state of muscle activity under which tremor was manifested, tremor was roughly divided into resting (R) and movement (M) types. Postural (P) type tremor implied that it only became manifest on maintaining a certain posture. When two components were present (this was frequently the case), note was taken of both. (2) Tremor was also classified into M_1, M_2 and M_3 categories, respectively, when it involved muscles of one, two or more joints. Tremor involving proximal muscles of the trunk was described as S_{1-4} ($_{1-4}$ indicating number of tremor muscles) and that occurring in neck muscles denoted by N. However, tremor of the neck was deliberately excluded from the study since the innervation of the neck muscles is intricate (bilateral innervation) and this makes the treatment of tremor occurring in these areas quite sophisticated. (3) On determining the frequency range of the tremor in each patient, the tremor was placed in one of three categories according to its frequency, namely, C_3 (less than 4 Hz), C_2 (4 to 7 Hz) and C_1 (greater than 7 Hz). (4) After determining the range of amplitude of the tremor by various loading tests in each patient, the tremor was similarly allocated to one of three categories according to its maximum amplitude, namely, A_1 (less than 300 μV), A_2 (300 to 600 μV) and A_3 (more than 600 μV). In evaluating the patients' ability for daily life (ADL), attention was focused on motor function in the upper limb on the affected side. Thus disability for drinking water and for writing was each rated on a three-point scale (0, 1, 2), and according to the value of summated ratings, patients were classified into one of five grades of ADL, 0–4. Each case of tremor with its component factors (including ADL), as classified in the above mentioned manner, was thus categorized in terms of a sequence of symptoms. For example, Case 1 is expressed by the following sequence: 57♂ 78-8-10, (Rt-Vim), Lt-M > P > R (D,L,P,B,T,F,E)$_7$$M_3S_3C_3A_3$ ADL$_4$ PCVD 212⊙. In this case the patient was a 57-year-old man who underwent a right Vim thalamotomy on August 10, 1978. He had tremor of movement (M), postural (P) and resting (R) types, occurring in this order of severity, mainly in the left upper limb. The distribution of the affected muscles was the flexors (B) and extensors (T) of the upper arm, flexors (F) and extensors (E) of the forearm and three proximal muscles of the trunk (S_3), that is, deltoid (D), latissimus dorsi (L) and pectoralis major (P), totalling 7 groups of muscles (M_3). The tremor frequency was below 4 Hz (C_3), the amplitude was above 600 μV (A_3) and ADL were markedly impaired (ADL$_4$). This case was of post-CVD tremor which was successfully abolished with a therapeutic lesion of 212 mm^3 in the predicted volume (*see below*).

Operative Procedure

As details of our operative procedure have already been described in previous reports (Ohye, Fukamachi *et al.*, 1977; Ohye and Narabayashi, 1979) mention will only be made of essential aspects.

Since the first operated case in 1972, the operation has been conducted by the same operator (C.O.) using Leksell's apparatus and microelectrodes. Twenty-one cases in the early stages of our study (July 1972 to August 1975) underwent subthalamothalamotomy, while 42 late cases (August 1975 to August 1978) were subjected to Vim thalamotomy. The third ventricle is first identified radiographically (pneumoventriculography; CT scanning since 1976) and then the tentative target is determined. Two semimicroelectrodes (outer diameter 0.6 mm, tip about 10 μm, interpolar distance 0.2 to 0.3 mm and electrical resistance about 50 to 100 kΩ) are introduced into the brain parallel with the frontal (Fukamachi *et al.*, 1977) or sagittal (Nakajima *et al.*, 1978) planes for the quantitative estimation of the neural noise level. An attempt is then made to identify somaesthetic neurons, especially kinaesthetic

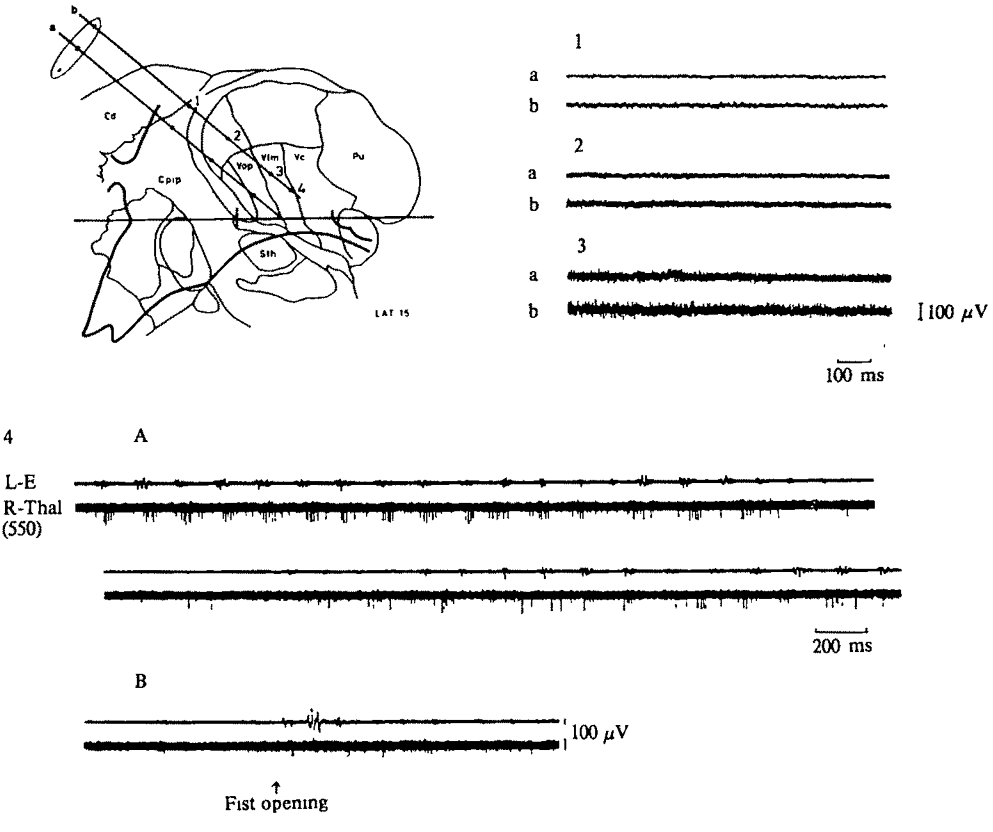


FIG. 1. Illustration for physiological identification of the Vim nucleus in a case with tremor type parkinsonism. Two semimicroelectrode trajectories (a,b) toward the tentative target area are shown with a sagittal plane reproduced from Schaltenbrand and Bailey's atlas (S.1 15.0) (1959) and a lateral view of the third ventricle in the upper left corner. A horizontal line and a short vertical line indicate the intercommissural line and its midpoint, respectively. In the upper right corner, three different patterns of background neural noise level recorded at the points 1, 2 and 3 shown in the upper left drawing are demonstrated (1 = white matter between caudate nucleus and thalamus; 2 = dorsal thalamus; 3 = ventral thalamus) Note that the background neural noise level is highest in the presumed Vim area (3b) 4 Multiple spike discharges recorded from the presumed right Vim nucleus (R-Thal) at a point 550 μm above the tentative target point, and EMG (*upper trace*) from the left forearm extensor muscles (L-E) are shown. A. The rhythmic discharges in the right Vim nucleus are almost time-locked with the peripheral spontaneous tremor and when the peripheral tremor ceased, the rhythmic discharges disappeared. B. The same multiple spike discharges increased on voluntary movement (fist opening). Cd = caudate nucleus. Cpip = posterior limb of internal capsule. Pu = pulvinar Sth = subthalamic nucleus. Vc = nucleus ventrocaudalis. Vim = nucleus ventrointermedius. Vop = nucleus ventro-oralis posterior.

neurons (Ohye and Narabayashi, 1979) responding to natural peripheral stimuli (passive and active joint movement) and thereby to define the upper and lower borders of the Vim nucleus in the thalamus. An example of the physiological data obtained in a case of parkinsonism is shown in fig. 1 to illustrate our usual method of identification of the target area. An investigation is also made of the motor and sensory effects of high and low frequency electrical stimulation of the thalamus. On the basis of these physiological data, an outline of the Vim nucleus of the thalamus in each case is clarified in relation to the position of the electrode tip. Finally, taking into consideration the predetermined features of the tremor, thermocoagulation is performed invariably for 10 s at 65° C with two coagulative needles of 4 mm effective length and 3 mm separation, positioned so that the real target is included between them. The tremor is usually abolished, at least in one part of the extremity, by the first coagulative lesion but if not totally, additional coagulative lesions are then placed in various directions within a cylindrical zone, 3 mm in radius, until it is completely abolished. In the earlier cases of this series, the therapeutic lesion was made with two coagulating needles of 6 mm effective length held in place 4 mm apart.

Determination of the Location of the Therapeutic Lesion and the Predicted Volume of the Whole Lesion

During the follow-up period, which was up to ten years, there were two fatalities, one case each of Parkinson's disease (six years after operation) and OPCA (five years after operation), but we did not have the opportunity to identify histologically the site of the coagulative lesions in either. In no case, therefore, was the coagulative lesion confirmed histologically. Coagulative lesions in individual cases, which were to be placed centred around the physiologically identified thalamic Vim nucleus, were delineated by projecting their image as outlined by intraoperative pneumoventriculography to the frontal and lateral planes using an intercommissural (IC) line, the anterior border of the posterior commissure and the midline as reference lines. With Leksell's apparatus (which ensures high frequency thermocoagulation at a strictly controlled temperature), a lesion can be produced that is almost confined to the region between the two coagulating needles under fixed conditions of 65° C and 10 s. It is possible, therefore, to obtain an estimate of the predicted volume of the whole lesion (PVL). We calculated the PVL, including the volume of tissue destroyed mechanically by the coagulation needles themselves, by the formula shown in fig. 2.

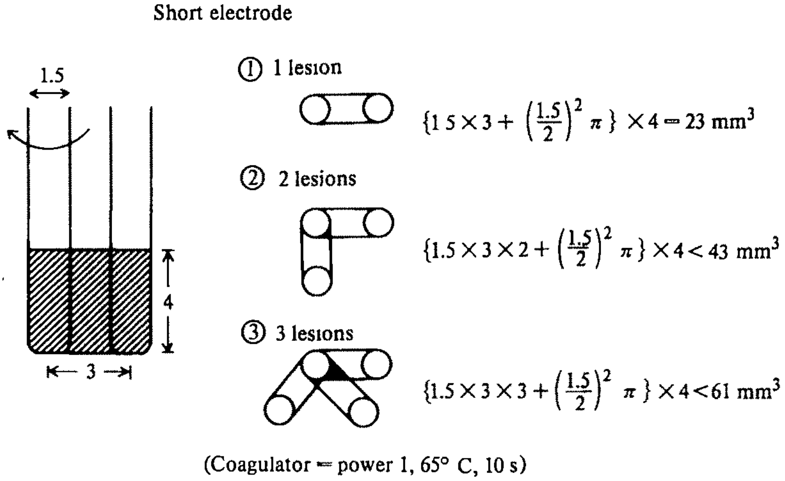

Short electrode
1.5
4
3
① 1 lesion
$\{1.5 \times 3 + \left(\frac{1.5}{2}\right)^2 \pi\} \times 4 = 23\ \text{mm}^3$
② 2 lesions
$\{1.5 \times 3 \times 2 + \left(\frac{1.5}{2}\right)^2 \pi\} \times 4 < 43\ \text{mm}^3$
③ 3 lesions
$\{1.5 \times 3 \times 3 + \left(\frac{1.5}{2}\right)^2 \pi\} \times 4 < 61\ \text{mm}^3$
(Coagulator = power 1, 65° C, 10 s)

FIG. 2. Formula used for calculating the predicted volume of coagulative lesions (PVL). A unit of thermocoagulation is invariably performed for 10 s at 65° C between a pair of coagulation needles (1.5 mm diameter) of 4 mm effective length and 3 mm separation as shown on the left (hatched area). In the centre, a plan view of the needles and lesions is shown schematically. As the black area in the diagrams is calculated more than once, the actual PVL is slightly smaller than the calculated value

RESULTS

Analysis of Operative Results

The operation was performed a total of 57 times in 51 cases (6 underwent reoperation) with the results indicated in Table 2. The outcome of operation was assessed clinically as well as on the basis of electromyography performed around two weeks after operation and from postoperative cinematographic records. In the 6 reoperated cases, the results of the second operation only were considered.

TABLE 2 RESULTS OF OPERATION*

Results	*Cases of Parkinson's disease*	*Cases other than Parkinson's disease*	*Total*
Complete abolition	19	25	44
Slight residual	4	5	9
Residual	0	2	2
Recurrence	1	1	2
			57

* Reoperation 6 Cases.

(1) In 44 cases, operation resulted in complete abolition of tremor. (2) Nine cases were found to have either transient episodes of tremor (although not a clinical problem) or slight partial residual tremor postoperatively. Four of these 9 cases were of Parkinson's disease; one had occasional tremor-like movements of the first toe of the affected lower limb postoperatively; 2 others showed irregular transient bursts arising from the flexor muscles of the upper arm; the remaining case had slight tremor involving the flexors of the leg. In all these 4 cases the tremor-like movements were controlled by drug therapy (L-DOPA). Another 2 of the 9 cases were of tremor complicated by intention myoclonus; in both cases the intensity of myoclonus decreased after operation facilitating their ADL considerably, but because of the similarity between the specific grouped discharges of tremor and myoclonic discharges, no conclusive statement could be made as to whether tremor was abolished completely by operation. The remaining 3 cases comprised 2 with idiopathic tremor and one with writer's cramp. In all these 3 cases, transient irregular grouped discharges occurred postoperatively. These 9 cases are still under follow-up observation, there having so far been no overt increase of tremor. The result of operation is thus considered satisfactory. (3) There were 2 cases in our series in which tremor, abolished immediately by operation, recurred one to two weeks postoperatively, necessitating reoperation. One of these 2 cases was of idiopathic tremor (22 yrs, female) and the other was of Parkinson's disease (62 yrs, male). The presumed cause of therapeutic failure was inaccuracy in the location of the

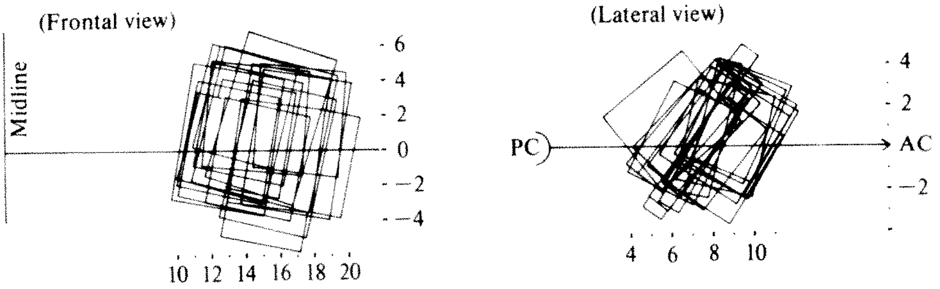
coagulative lesion in the latter case and too small a volume in the former. (4) In 2 other cases, tremor persisted unequivocally both intra- and postoperatively. These 2 cases were of post-CVD and post-traumatic tremor, both having been treated before the introduction of CT scanning. In the post-CVD tremor case (43 yrs, female), structural changes in the thalamus, due presumably to previous cerebrovascular damage with a resultant unusual neural noise pattern in the thalamus, made it impossible to identify the Vim nucleus electrophysiologically. This led to persistence of tremor, which mainly involved proximal trunk muscles, although it was of reduced amplitude after the production of the therapeutic lesion. In the post-traumatic tremor case (59 yrs, male) the Vim nucleus could not be defined clearly because of marked enlargement and displacement of the third ventricle. The tremor was not completely abolished postoperatively, although diminished in intensity. As exemplified by these 2 cases, structural changes of the thalamus, with a resultant failure to show a normal neural noise pattern, are likely to have occurred in cases of tremor of post-CVD or post-traumatic type (Isobe *et al.*, 1976/77). Thus in 57 operative cases, excluding 2 scheduled to be reoperated, relief of tremor was achieved in all in which the Vim nucleus could be identified by electrophysiological means at operation (disregarding some difference in the volume of the coagulative lesion). Among these 57 cases, 4 experienced complications of operation, namely, postoperative meningitis (61 yrs, male, idiopathic tremor), intraventricular haemorrhage incidental to intraoperative ventriculography (67 yrs, female, tremor of Parkinson's disease), postoperative perioral paraesthesiae (62 yrs, female, Parkinson's disease) and a slight postoperative motor paresis of the affected limb (21 yrs, female, idiopathic tremor). However, these cases were all treated in the early stages of this study and the postoperative course was quite uneventful thereafter without any serious complications.

Relationships between the Location and Volume of the Coagulative Lesion and the Various Tremor Characteristics

Fig. 3 gives a diagrammatic representation of coagulative lesions on a standardized coordinate system, separately shown for early and late operations. Fig. 4 shows the results of operation in relation to the predicted volume of the coagulative lesion (PVL) (plotted on ordinate) in the entire series. As is obvious from these figures, coagulative lesions were smaller in late operation cases, in which no coagulative lesions were placed in the subthalamic area. Especially in 15 late cases, coagulative lesions were around 40 mm^3 in volume and were thought to be within the confines of the Vim nucleus. These correctly placed intrathalamic lesions brought about a complete abolition of tremor and the effect of operation has been long lasting. An investigation was also made of the relationships between PVL and individual tremor characteristics in 42 later cases of Vim thalamotomy.

Relation between PVL and type of tremor (fig. 5). Cases with resting tremor mostly also develop this on actively maintaining a posture but never during movement. Such cases were all of Parkinson's disease except for one in which the diagnosis

A Earlier 21 operations



B Later 37 operations

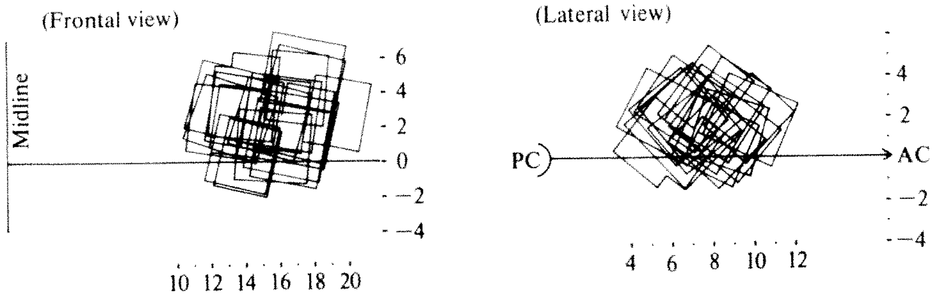


FIG. 3. Diagrammatic representation of the coagulative lesions in 21 cases operated at an early stage in the study (A) and in 37 cases operated more recently (B). Long needles of 6 mm effective length positioned 4 mm apart were used in the early cases, while short needles of 4 mm effective length positioned 3 mm apart were employed in the later cases. They were delineated by intraoperative pneumoventriculography and projection onto the frontal and lateral planes using the intercommissural line (PC = posterior commissure, AC = anterior commissure), and the anterior border of the posterior commissure and the midline for reference. Note that in the early stage, the unit lesion is larger and the selected target is slightly deeper than in the later stages.

could not be firmly established. Tremor in these parkinsonian cases was successfully abolished with a small coagulative lesion. A postural type of tremor was seen in 2 cases each of juvenile Parkinson's disease, essential tremor and post-traumatic tremor. In these, tremor was particularly conspicuous while actively maintaining a posture (or assuming a particular position) and was abolished by a moderate (70 mm^3) or smaller therapeutic lesion. Tremor of movement type, by nature, contains a component of postural tremor. Some tremors of this type were abolished by a small coagulative lesion, while others required a therapeutic lesion of moderate or larger size. Particularly in 2 cases (both post-CVD) in which tremor was manifest at all times (both during movement and at rest), a large therapeutic lesion was necessary.

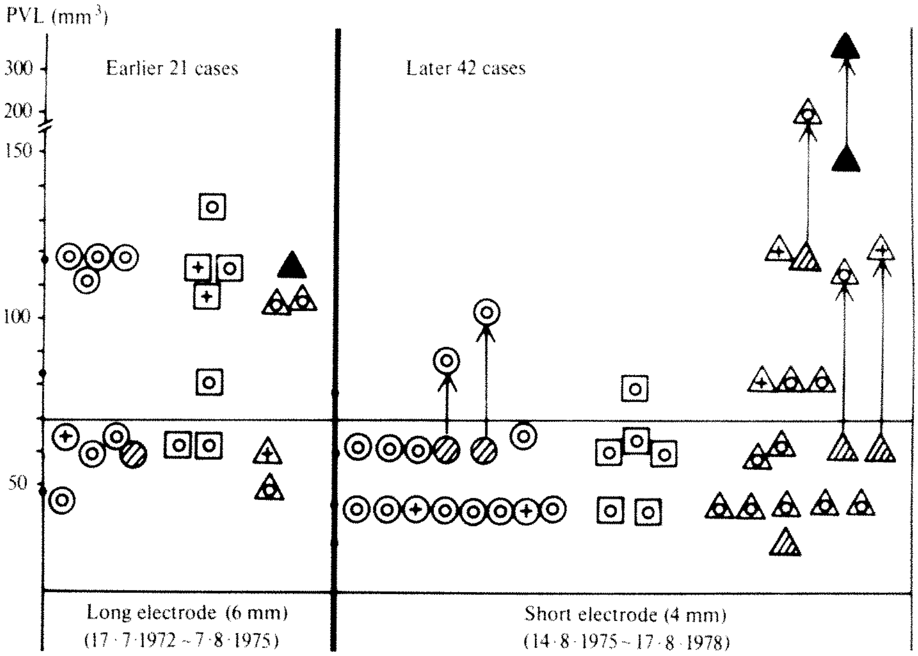


Fig. 4. The results of operation in the entire series of cases are shown in relation to the predicted volume of the lesion (PVL). The ordinate is the PVL and the abscissa shows individual cases. The earlier 21 cases (*left*) and the later 42 cases (*right*) are separated by a thick vertical line. Three different types of tremor (resting, postural and movement types) are grouped and shown in this order from left to right in the early and late cases, respectively: ○ = resting type; □ = postural type; △ = movement type; o = complete abolition; + = slight residual tremor; ▲ = residual tremor; ▨ ▨ = recurrence of tremor. The arrows indicate the reoperated cases. For convenience, the horizontal line at 70 mm³ in the figure indicates a coagulative lesion regarded as of moderate size.

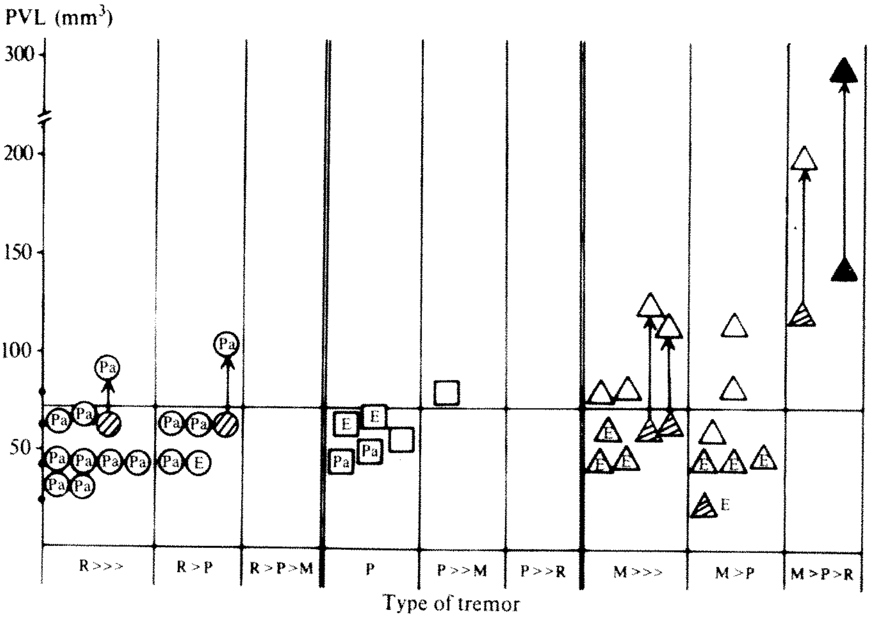


Fig. 5. Relation between predicted volume of the lesion (PVL) (ordinate) and tremor type in the later operated cases; resting (*left*), postural (*centre*) and movement tremor (*right*). The cases which show two types of tremor are indicated by a sign of inequality (>). Tremor patterns of the type R > P > M and P ≫ R did not occur in this series. Pa = Parkinson's disease; E = essential tremor; R = resting type; P = postural type; M = movement type. Symbols as in fig. 4.

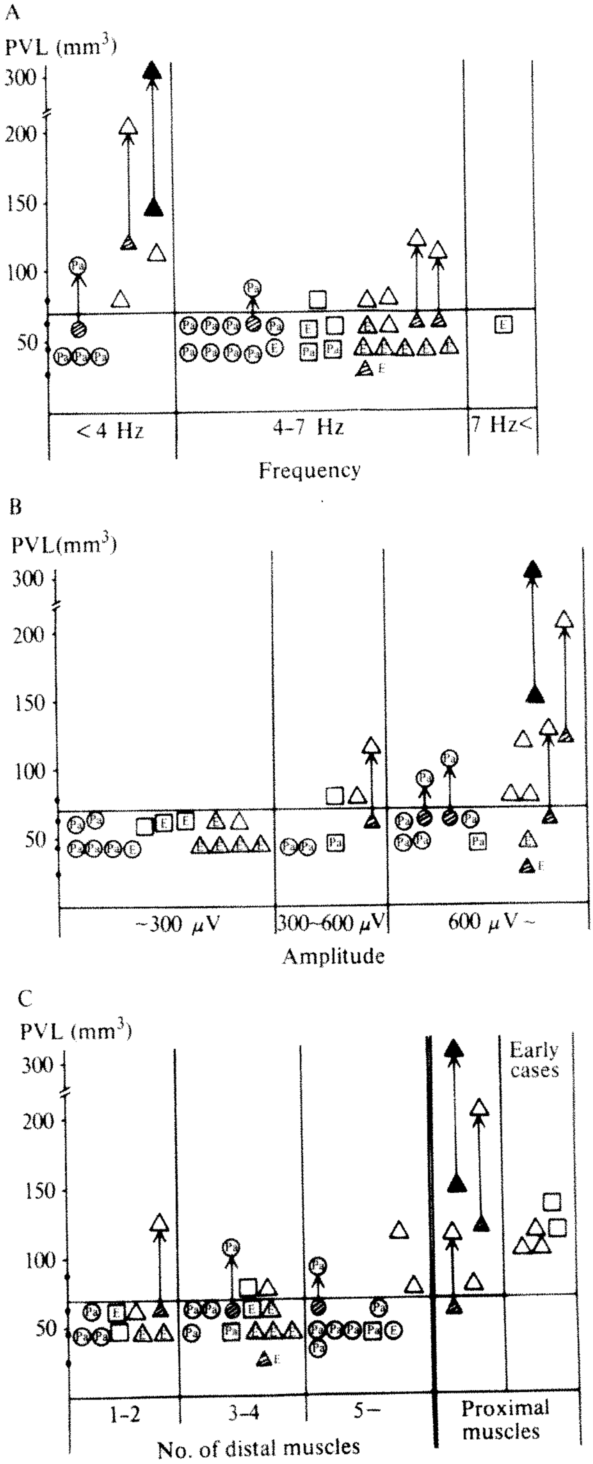


FIG. 6A. Relation between predicted volume of lesion (PVL) (ordinate) and tremor frequency subdivided into 3 groups (abscissa) in later operated cases. B, relation between PVL (ordinate) and tremor amplitude subdivided into 3 groups (abscissa) in later operated cases. C, relation between PVL (ordinate) and the distribution of tremor subdivided into 4 groups (abscissa) in later operated cases. 1–2, 3–4, and 5– = the tremor involved 1–2, 3–4 and more than 5 muscle groups, respectively. The PVL for early cases with involvement of proximal trunk muscles is shown in the panel furthest to the right. Symbols as in fig. 4.

Relation between PVL and the frequency of tremor (fig. 6A). Most tremors are within a frequency range of 4 to 7 Hz, and they are relieved by a relatively small lesion. On the contrary, coarse tremor with a frequency of less than 4 Hz required a larger lesion. Most such cases were of movement type (designated by triangles in fig. 6A). Some examples of Parkinson's disease may be associated with coarse oscillation of less than 4 Hz, but relieved by a small lesion. Essential tremor is around 7 Hz in frequency in many instances and is also easily relieved by a small lesion.

Relation between PVL and the amplitude of tremor (fig. 6B). The tremor of Parkinson's disease varies widely in amplitude, while essential tremor is of low amplitude in many instances. In general, the larger the amplitude of the tremor, the larger is the coagulative lesion that is required, while the low amplitude group is without exception well controlled by a small lesion.

Relation between PVL and the distribution of the tremor (fig. 6C). In cases in which tremor was limited to the limbs, there was no distinct relationship between PVL and the number of muscle groups involved. By far a largest coagulative lesion was required, however, in those cases of tremor involving proximal trunk muscles. PVL values for those early cases of tremor involving proximal trunk muscles were all around 120 mm^3. It is noteworthy that there are no tremor cases with proximal muscle involvement who are relieved by a small lesion.

Relation between PVL and the aetiology of tremor (fig. 7). The tremor of

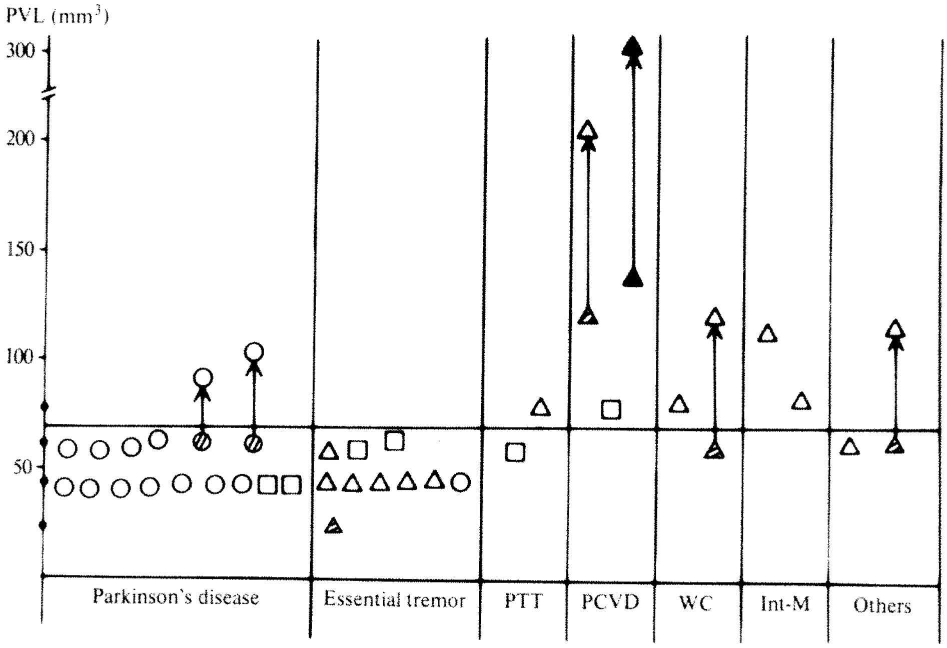


FIG. 7. Relation between predicted volume of lesion (PVL) (ordinate) and the aetiology of the tremor, subdivided into 7 groups (abscissa) in later operated cases. PTT = post-traumatic tremor; PCVD = tremor following cerebrovascular lesions; WC = writer's cramp (tremor type); Int-M = tremor combined with intention myoclonus. Symbols as in fig. 4.

Parkinson's disease and essential tremor could be successfully abolished with a small or medium-sized (70 mm^3) coagulative lesion. By contrast, post-traumatic and post-CVD tremor required for its control a medium-sized or large coagulative lesion and even a huge lesion in occasional cases. A moderate or larger volume lesion was also necessary for the successful treatment of writer's cramp, tremor associated with intention myoclonus, and tremor accompanying intracranial tumour.

Minimum Effective Volume for Coagulative Lesions

In one case of essential tremor we produced a small coagulative lesion, 23 mm^3 in volume (effective electrode length 4 mm; interelectrode distance 3 mm), by a single coagulative manipulation. This case, a 20-year-old woman, was expressed as Lt-$M \geq P\ (B,T,F,E)_4 M_2 S_0 C_2 A_2$ ADL$_1$ ET. More particularly, the tremor occurred during movement (M) and when maintaining a posture (P), involving 4 groups of muscles of the left arm (B: biceps brachii, T: triceps brachii, F: forearm flexors, E: forearm extensors) (M_2); the tremor frequency was 4 to 7 Hz (C_2) and the amplitude 300 to 600 μV (A_2); proximal trunk muscles were not involved (S_0). The Vim nucleus was identified at operation by characteristic background activity and insertion of recording electrodes into the nucleus was followed immediately by lessening of tremor. As high frequency electrical stimulation of the nucleus resulted in suppression and cessation of grouped discharges on EMG, an attempt was made to produce a small coagulative lesion of a 23 mm^3 predicted volume to this region. The operation ended with this manipulation since it brought about complete abolition of

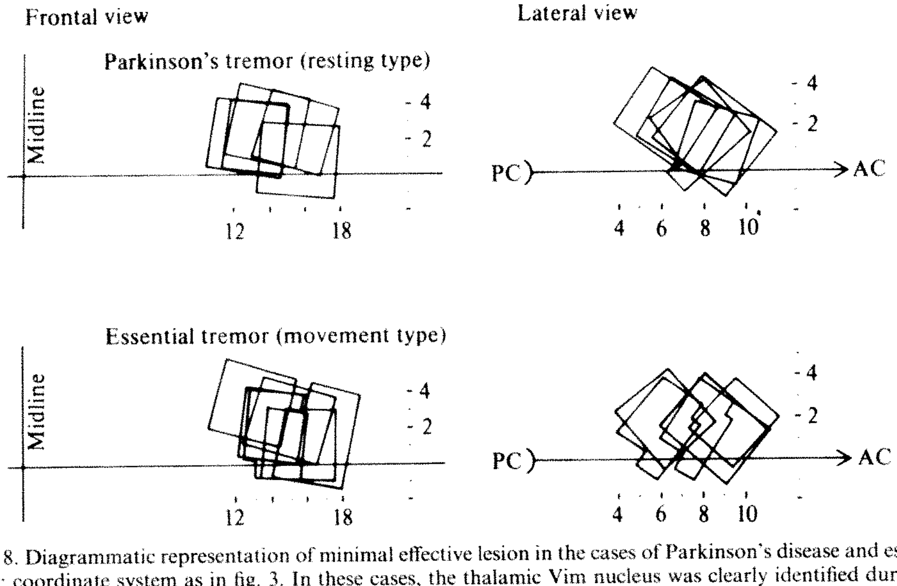


FIG. 8. Diagrammatic representation of minimal effective lesion in the cases of Parkinson's disease and essential tremor; coordinate system as in fig. 3. In these cases, the thalamic Vim nucleus was clearly identified during the operation and a small coagulative lesion about 40 mm^3 assumed to be located almost wholly within Vim nucleus. The shift of each coagulative lesion may be due to individual variations in the location of Vim in the thalamus.

tremor, which was not provoked even by several manoeuvres in the operation room. Unfortunately, however, the tremor reappeared about two weeks after operation. Although the recurrent tremor was mild in severity, being expressed as Lt-M $\geqslant$ P $(F,E)_2M_2S_0C_2A_1$ ADL_0 ET, reoperation was successfully undertaken. Experience in this case suggests that in order for a coagulative lesion to prove effective definitively in the relief of tremor, its volume must exceed a certain level, even if it is placed correctly within the Vim nucleus. Fig. 8 represents the locations of small coagulative lesions produced in cases of parkinsonian tremor and of essential tremor. These lesions placed within the Vim nucleus were less than 43 mm^3 in volume but, nevertheless, were effective in completely abolishing the two types of tremor. All these facts led us to conclude that the minimum effective volume for a coagulative lesion for those tremors, of low to medium amplitude, 4 to 7 Hz in frequency and involving the distal portions of the extremities only, is estimated at around 40 mm^3, provided that it is produced within the confines of the identified Vim nucleus by our operative procedure.

DISCUSSION

The present results for stereotaxic operation with application of physiological techniques showed that satisfactory relief of various types of tremor was achieved by a small coagulative lesion measuring about 40 mm^3, mainly localized within the Vim nucleus of the thalamus. However, no direct histological examination was available and the actual site of coagulation and the volume of the lesion have not been confirmed. Therefore, the decision as to the site of coagulation was based on physiological identification of the Vim nucleus (Ohye, Maeda *et al.*,1977; Ohye and Narabayashi, 1979). In view of the physiological data (measurement of neural noise, identification of kinaesthetic neurons and the effect of electrical stimulation) obtained in the frontal (Fukamachi *et al.*,1977) and sagittal (Nakajima *et al.*, 1978) planes by using two microelectrodes and presumed functional localization within the Vim nucleus, it is possible to localize the coagulating needle within a particular portion of the nucleus. In practice, neither paralysis nor sensory disturbance of the affected limb occurred postoperatively, so that extension of the coagulative lesion to the thalamic Vc (nucleus ventrocaudalis) nuclei or the posterior limb of the internal capsule is almost completely excluded. The lesion is therefore likely to be sufficiently well localized (*see* Appendix).

Various problems are nevertheless encountered in the measurement of the volume of the coagulative lesion. As to the postmortem findings of coagulative lesions, Walsh (1966) employed the same operative method as ours and described a wide variation in the volume of the lesion. In their apparatus, however, the two electrodes for coagulation were placed with a separation of 8 to 10 mm and coagulation was produced at 52° C, in contrast to our procedure. Using Leksell's coagulation apparatus, we generally made a lesion with two needles separated by 3 mm at 65° C for 10 s. According to the results of experiments that we have made using egg white, an almost circumscribed lesion was consistently produced between the two needles. Simple calculations based on this fact yielded a predicted volume for the coagulative lesion to be used in practical terms. We have furthermore produced an experimental model of the tremor in monkeys (Poirier *et al.*, 1969; Ohye, Imai *et al.*, 1979), by producing a localized coagulative lesion in the tegmental region of the midbrain by a method exactly identical to the one used for human stereotaxic operations. The brains of these monkeys with tremor were examined and the extent of the lesion approximated to that predicted. Although this conclusion is based on the findings obtained in monkeys and may not be directly applied to the human thalamus, in view of the difference in tissue structure, including vascular architecture, it appears to be possible to produce a coagulative lesion in the Vim nucleus with a range of error of approximately ±0.5 mm. Further, an approximate correlation appears to be present between the predicted volume of the coagulative lesion (PVL) obtained by a simple calculation and the actual size of the coagulative lesion (Nakajima *et al.*, 1981).

The relationship between the predicted volume of the effective coagulative lesion and each component of tremor will now be discussed from the clinical standpoint. In our correlative study (*see* fig. 6), it can be seen that cases with movement type tremor, except for essential tremor (triangle in fig. 6), required a relatively large coagulative lesion in Vim thalamotomy. They are mainly the cases of post-CVD tremor with high amplitude, low frequency and involvement of the trunk muscles. Among various tremor characteristics, it seems likely that its distribution (fig. 6C) and amplitude (fig. 6B) are closely correlated with the effective PVL, because no cases with tremor affecting proximal muscles were treated by a small lesion and no large lesion was necessary for cases with tremor of small amplitude. In cases with tremor distributed over the proximal trunk muscles, coagulative lesions tended to be larger, probably because the functional localization of the portion related to proximal trunk muscles within the thalamic Vim nucleus remains uncertain. The functional localization within the thalamic Vc nucleus in man was studied in detail by Jasper and Bertrand (1964), G. Bertrand *et al.* (1967, 1969) and Guiot *et al.* (1973) and these results have been utilized for thalamotomy. No detailed reports, however, are yet available on the functional localization of kinaesthetic neurons within Vim. According to our own experience in the identification of kinaesthetic neurons within Vim, the units in this nucleus appear to be arranged primarily in a dorsolateral to ventromedial direction corresponding to a lower limb-upper limb-face sequence, as in the Vc nucleus. However, truncal units were not included in this sequence and were rarely encountered. Instead, it seemed as if they were sited separately in the dorsal and posterior part of Vim, if at all. Further clarification of the functional localization within this nucleus in the future would make it possible to treat tremor distributed over the proximal trunk and neck muscles with smaller lesions.

As to tremor amplitude, this is to some extent dependent on spinal reflex mechanisms involving the gamma loop in a sense that tremor is modified by several peripheral factors. On the other hand, an increase in the amplitude of tremor is considered to represent a deterioration of the disease state. Tremor amplitude is thought to be related to quantitative factors such as the number of cells involved and the degree of synchronization within those CNS components participating in the maintenance of the tremor. In our experience, the fact that cases with large amplitude tremor required a large coagulative lesion in Vim suggests that this nucleus is one of the important structures in tremor mechanisms in terms of amplitude.

The type and frequency of the tremor, recognized as further fundamental characteristics of a tremor, are not apparently related to PVL in Vim thalamotomy. Thus Vim appears to represent a common neural mechanism for all types of tremor in terms of its localization and amplitude. This nucleus, one of the subdivisions of the thalamic nuclei, is demonstrable only in higher animals (above monkey) (Hassler, 1977; Ohye, 1978), and is located between the Vo (nucleus ventro-oralis) and Vc (nucleus ventrocaudalis) groups of nuclei, and lateral to the Ce (nucleus centralis) group. In man, relatively large angular cells measuring 30 to 50 μm in diameter, stained intensely by the Nissl method, are found in a more scattered distribution than in Vo and Vc. Distinction between them is easily made histologically (Dewulf, 1971; Van Buren and Borke, 1972; Hirai *et al.*, 1982). Although the fibre connections and the functional properties of Vim in man are as yet obscure (Hassler *et al.*, 1979), the present results reveal that localized destruction of this nucleus almost certainly results in a selective and permanent disappearance of the various forms of tremor and never causes any detectable sensory or motor disturbances postoperatively. In one case who complained of perioral paraesthesiae after operation, the coagulative lesion was placed somewhat more posteriorly (probably in part of the Vc nucleus) than in the other cases.

In the treatment of various forms of tremor, therefore, such procedures on the Vim nucleus have been safer and more effective than for any other sites previously selected (Gillingham, 1962; Andy *et al.*, 1963; Spiegel *et al.*, 1963; Mundinger, 1965; C. Bertrand *et al.*, 1973). Moreover, according to this retrospective analysis, preoperative planning of the site and volume of the coagulative lesion is now possible by analysing the tremor with EMG to assess its distribution and range of amplitude. Furthermore, after the introduction of CT scanning, the anatomical structures through which the electrode will pass intraoperatively are visualized (Ohye, Nakajima *et al.*, 1981) and any structural changes (in cases of tremor following cerebrovascular disturbance) are demonstrated preoperatively (Isobe *et al.*, 1976/77), and physiological studies identify the thalamic Vim nuclei even more definitely. Further elucidation of the neural mechanisms of tremor that involve the thalamic Vim nucleus is expected by this small localized thalamic lesion.

APPENDIX

After the preparation of this manuscript, a case with essential tremor died accidentally about two months following a left nucleus ventro-oralis posterior (Vop)-Vim thalamotomy. Although this

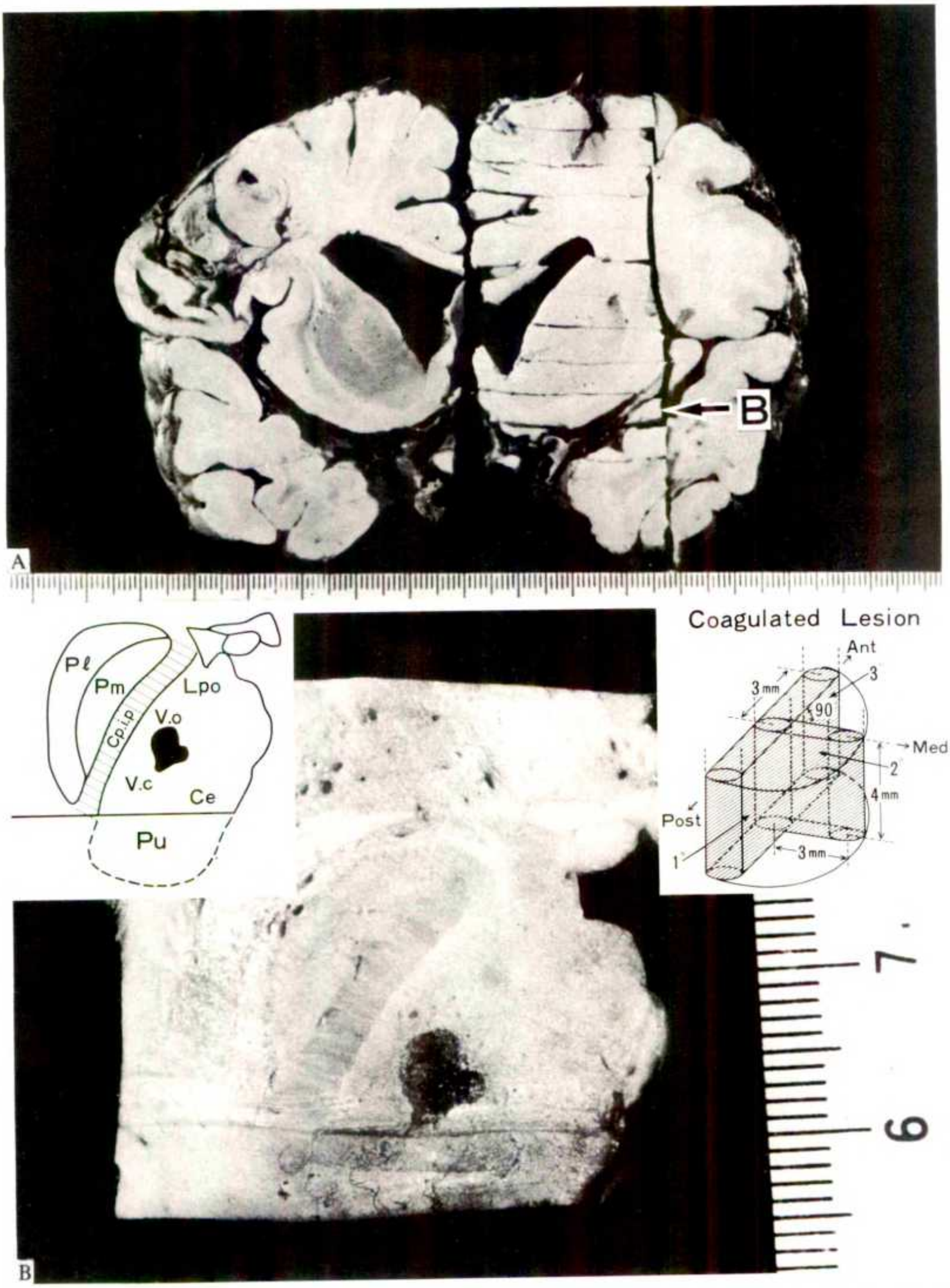


FIG. 9A. Coronal brain section at the level of the head of the caudate nucleus in the case described in the Appendix. The ventricular system is markedly dilated, probably because of a previous intracerebral haematoma in the right parietal lobe. The left cerebral hemisphere, which contained the operative lesion (on right of fig.) was cut into 11 horizontal sections, each about 5 to 7 mm thick. An arrow (B) indicates the tenth horizontal section from the top, passing through the lower border of the thalamus. B, upper surface of the tenth horizontal section shown in A, containing the coagulative lesion. A schematic drawing of this section is shown in the upper left corner (its posterior part is added). The predicted lesions made in this case are shown schematically in the upper right corner, where the coagulation needles (1.5 mm diameter) of 4 mm effective length and 3 mm separation are shown in a three dimensional view. Pu = pulvinar. Vc = nucleus ventrocaudalis. Vo = nucleus ventro-oralis. Lpo = nucleus lateropolaris. Pm = medial pallidum. Pl = lateral pallidum. Cpip = posterior limb of internal capsule. Ce = central thalamic nuclei.

patient is not included in the present study, the actual site and volume of the coagulative lesion were examined at autopsy and demonstrated in horizontal section of the thalamus, as shown in fig. 9. In this case, three coagulations were made on the physiologically defined Vim and Vop nuclei. The first lesion was made in Vim and the second placed in an anteromedial direction by turning the peripheral (posteriorly placed) needle around the central needle to a position 90 deg anteromedial to the first lesion. The third lesion was placed in a direction 180 deg anterior to the first by the same method. After the operation, the patient's writing was quite normal, without tremor. The actual coagulative lesion was localized as predicted and located in the Vim and Vop nuclei. This was confirmed by histological studies.

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NOTICES OF RECENT PUBLICATIONS

Genetic Basis of the Epilepsies. Edited by V. Elving Anderson. W. Allen Hauser: J. Kiffin Penry and Charles F. Sing. 1982. Pp. 396. Price $59.84.

This book arose out of a conference on the Genetics of Epilepsy and it is composed of papers revised afterwards in order to record points raised in discussion during the meeting. The aim of the editors was to produce a book which would be of value to specialists concerned with epilepsy (for example, neurologists, physiologists, psychologists, epidemiologists and geneticists), which would stimulate and encourage them into further research, and which would engender collaborative studies. The individual authors were therefore encouraged to speculate about future prospects.

These aims are achieved and the book is stimulating. What is missing is an account of background work on the genetics of epilepsy. It is therefore essential for the reader to have a prior secure knowledge of epilepsy; the book is not one for students.

The book is divided into four sections. The first describes clinical aspects of epilepsy; its classification; its frequency and its relation to age and the maturation of the electroencephalographic pattern. Next there is a section on family studies when personal work is described Four noteworthy chapters are those by Doose and Gundel on genetic studies on 4 to 7 Hz rhythms in the electroencephalogram, by Doose on the genetics of photosensitive epilepsy, and the two by Janz and Beck-Mannagetta reporting their work on the occurrence of epilepsy and febrile convulsions in the offspring of epileptic parents. One general criticism of the reported studies is that previous work by others is rather cursorily reviewed. It is also disappointing that Andermann does not provide evidence for her view that different types of epilepsy are due to polygenic inheritance, but merely refers to her published work. There is good evidence (E. Slater and V. Cowie, *The Genetics of Mental Disorders*, Oxford University Press, London, 1971) that single genes (always autosomal dominant) may account for some types of epilepsy and certainly for some EEG patterns, and that multifactorial inheritance is likely to be the cause of other types of epilepsy. One difficulty about reaching conclusions about the inheritance of epilepsy is the fact that clinical manifestation is age dependent. This is particularly striking for centrencephalic petit mal and febrile convulsions and there is still controversy as to whether the predispositions to these conditions are caused by a single autosomal dominant gene or by many genes, of little effect individually. The genetic findings in these two types of epilepsy are reviewed by Tsuboi and Ward.

The last two sections are concerned with basic scientific approaches to the causation of epilepsy. The chapters include an account of audiogenic epilepsy in susceptible mice by Seyfried and its use as a model for the study of epilepsy in general; the possibility of using DNA recombinant technology for the study of epilepsy (perhaps a little unrealistic at present) and a variety of statistical models for future research. Finally Murphy, in an elegant essay, reminds us to remember the clinical plight of the epileptic patient.

In summary, this book succeeds in what it sets out to do, namely to provoke and stimulate further research and to encourage collaborative studies. It does not provide a comprehensive critical account of the genetics of the epilepsies but it is a very useful book to accompany other reading.

SARAH BUNDEY

Cerebrovascular Diseases. Princeton Research Conference, 13. Edited by M. Reivich and H. I. Hurtig. 1983. Pp. 512. New York. Raven Press. Price $90.52.

Conference proceedings tend to have limited appeal even when they are produced within about twelve months of the meeting. Many contributions are light weight and the discussion is often omitted to speed up publication. The Princeton conferences over the last twenty-nine years have been exceptions to this rule and have become important sources of original material and ideas. This latest volume, recording the meeting held in March 1982, contains much data which is unlikely to appear elsewhere. Those attending were subjected to peer review of their offerings and the result is an even high standard of presentations on four new topics. The first part concerns NMR and PET scanning. Kuhl's data on the patchy regional defects of glucose metabolism in multi-infarct dementia is the most interesting clinically, the other contributions being mostly of technical importance. The second section deals in prognostic indications in cerebrovascular disease. The finding of the Cornell group that the level of blood sugar on admission even in nondiabetics with an acute stroke is predictive of poor outcome is the most striking 'message'.

There follows a series of papers on the potential for prevention of irreversible ischaemic damage. These discussions revolve around the roles of free fatty acids, lactic acid, preischaemic substrate levels and lipid peroxidation. No one hypothesis 'explains' all the features that trip the time bomb of ischaemic cell death, though Seisjo makes a strong case for local changes in free Ca^{++} having a pivotal role.

Finally there are some interesting studies on vessel wall damage due to experimental stenosis, platelet scanning of diseased vessels and clinical trials of low dose heparin in progressing stroke and the use of petrofluorochemicals.

The whole volume repays cover to cover reading, especially the discussion sections which often contain minipresentations of new data as well as Dr Yatsu's bright ideas. One of the other discussants introduces a new concept, that of the type III error in clinical trials when the grant body 'pulls the rug out' from under the study. Those interested in cerebrovascular disease research will want to borrow this book from their library.

M. J. G. Harrison

Clinical Neuro-Otology. By Peter Rudge. Clinical Neurology and Neurosurgery Monographs. 1983. Pp. 341. Edinburgh: Churchill Livingstone. Price £20 00.

Dr Rudge is a pioneer adventurer in a field of medicine hitherto poorly understood and beset by recondite problems. His precise and timely monograph is of unique value as the work of an experienced neurologist with the additional qualification gained through years of consultant practice in a neuro-otological clinic. The enormous advances that have been made in neuro-otological diagnosis over the past three decades have led to an ever growing demand for some up-to-date review of the whole subject as attempted in this long awaited book. The work is arranged in three distinct sections. Current knowledge of the anatomy and physiology of the VIII nerve and oculomotor systems is reviewed. Modern techniques of clinical assessment of the vestibular, oculomotor and auditory systems are thereafter described with special reference to their scope and value in diagnosis. The final section is concerned with specific diseases which may implicate the vestibular and auditory systems. An enormous amount of information has been compressed into a small space with excellent illustrations throughout, together with a comprehensive bibliography. The chapter on Vestibular Compensation and Management is especially timely as emphasizing the plethora of factors which may cause vertigo, the failure of understanding of which has resulted all too often in the giddy patient being labelled as psychiatric or functional. Certain opinions expressed are controversial as exemplified by the recommendation of promazine as 'the most useful vestibular sedative'. As a condition so commonly encountered in practice one would have welcomed a fuller description of the clinical features and abnormal neuro-otological findings in Vestibular Neuronitis including more recent work (Pfaltz, 1970; Friedmann and House, 1980). Errors are minor, the most unfortunate involving the descriptive text to fig. 5-33.

This is a very valuable book. It is well produced, readable and a bargain at the price quoted Dr Rudge has done clinical neurology a great service indeed in this important reading to be commended to all clinicians practising in this and related fields.

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M. R. DIX

Autonomic Failure: a Textbook of Clinical Disorders of the Autonomic Nervous System. Edited by Sir Roger Bannister. 1983. Pp. 666. Oxford University Press. Price £45.00.

The aim of this book is to provide clinicians in many fields with a guide to useful facts and tests of autonomic function. This text provides the important function of synthesizing physiological, pharmacological, pathological and neurochemical techniques which have been scattered in papers in diverse disciplines. Sir Roger Bannister is an ideal choice to undertake this task since he is at home in the basic science laboratory as well as the clinical autonomic laboratory and is also an active neurologist. He is amply supported by contributors who are all experts on the autonomic nervous system and all of whom are familiar with autonomic failure in human subjects.

The book is organized into three sections. The first is introductory and integrative, serving the function of introducing the topics and providing an overview. It contains a chapter on testing autonomic reflexes by the editor. This is followed by the major thrust of this text which is a detailed review of progressive autonomic failure (idiopathic orthostatic hypotension, Shy-Drager syndrome, and related disorders). The last section has several chapters on the dysautonomia of diabetes. The balance of other dysautonomias such as amyloid neuropathy, familial dysautonomia and autonomic failure of the elderly are contained in this section.

I thought that the choice of topics and authors was good and that the book covered a difficult field admirably. With a multiauthored approach, there is often some unevenness and individual biases. The editor has managed to provide a balance by judicious selection of contributors and also by juxtaposing chapters expressing alternative viewpoints. For instance, the chapter by Terence Bennett on 'Physiological investigation of diabetic autonomic failure' provides a critical evaluation of bedside tests of autonomic function and suggests that the interpretation of such tests is not as straightforward as suggested in the preceding chapter by D. J. Ewing. Similarly the status of plasma noradrenalin in autonomic failure is covered in several chapters and different viewpoints are expressed.

There are many excellent chapters. Ones I particularly enjoyed include that on 'Adrenergic receptors in autonomic failure' by Bleddyn Davies, which reviews facts and suggests mechanisms underlying phenomena such as denervation supersensitivity. The chapter on 'Plasma noradrenalin in autonomic failure' by P. S. Sever is very balanced, providing an excellent synthesis of the usefulness and limitations of plasma noradrenalin and addresses the question of noradrenalin in the context of pre- and postganglionic lesions. The chapter on 'Treatment of progressive autonomic failure' by Roger Bannister is brief but clearly and critically written.

This book has achieved the objectives of the editor. It contains a balanced and excellent collection of chapters. It provides the reader with a readily accessible reference source of useful tests of autonomic function. It also places in some perspective the usefulness and shortcomings of the noninvasive tests. Sir Roger Bannister is fully aware of the shortcomings of not having a recording of blood pressure (just knowing that there is no reflex bradycardia is not helpful if we do not know if there is a blood pressure overshoot). He has overcome this problem in part by monitoring the pulse volume during tests such as the Valsalva manoeuvre. He has also done a service by emphasizing in this text that these noninvasive tests are easy to do but complicated to interpret. He has also emphasized the current gaps in our knowledge. In particular, good quantitative tests of postganglionic function are only just being evolved. From the neurologist's standpoint, the 'black box' concept of autonomic testing is inadequate and hopefully by the next edition there will be more satisfactory techniques to quantitate postganglionic and regional neurological deficits. It is also hoped that in the next edition the neuropathological chapters will include published data on morphometric analysis of the autonomic nervous system in normal and abnormal man.

The cost of the book is rather high, but I would enthusiastically recommend it to neurological, neuroscience, and internal medicine libraries. I expect many neurologists will also purchase this for their own use.

PHILLIP A. LOW

Rehabilitation of the Neurological Patient. Edited by L. S. Illis, E. M. Sedgwick, H. J. Glanville. 1982. Pp. 499. Chicago and London: Year Book Medical Publishers. Price £22.50.

One of the largest groups of disabled people in the United Kingdom is those caused by neurological disorders. There are 140,000 patients with head injuries of whom 7,000 are severely affected, 500,000 with strokes and 50,000 with multiple sclerosis. Some patients—those with spinal injuries, the blind, the deaf and those with spina bifida—are superbly rehabilitated but for those suffering from head injuries or strokes there is no organized service, the service being organized on an *ad hoc* basis.

In the United Kingdom, while rehabilitation services were developed during the First World War in sheltered workshops by Robert Jones, this was not carried on until the advent of the Second World War when the collaboration between the forces established comprehensive services for head injuries and spinal injuries. Unfortunately there has not been comprehensive development in all forms of neurological rehabilitation and the United Kingdom has lagged behind Europe and the United States where the speciality of Rehabilitation for Neurological Disorders has progressed.

This book attempts to remedy this. Part I is excellent with some good, fundamental articles on plasticity of the adult nervous system. Unfortunately the second part, which deals with the specific problems, does not maintain the same high standards and tends to relate how the particular author deals with his patient rather than setting out general principles. Nevertheless there are excellent articles on the rehabilitation of strokes by R. Langton Hewer and on the management of the neuropathic bladder by M. J. Torrens and R. C. L. Feneley.

The whole book is thoroughly worthwhile and is essential reading for any neurologist who is involved in the rehabilitation of neurological patients.

J. R. SILVER

Lead versus Health. Sources and Effects of Low Level Lead Exposure. Edited by Michael Rutter and Robin Russell Jones. 1983. Pp. 379. Chichester: John Wiley. Price £18.50.

This book is a report on the proceedings of a symposium 'Low level lead exposure and its effects on human beings' organized by CLEAR in May 1982. There are contributions from most of the best known workers in the field (e.g. David, Lansdown, Moore, Rutter and Needleman). As expected it therefore presents an up-to-mid-1982 review of the present state of the evidence concerning lead effects.

The first part consists of data concerning sources of lead exposure and, not surprisingly, there is considerable discussion and disagreement about the importance of lead in petrol as a source of exposure. A section on experimental studies of possible relevance follows and finally the important question of neuropsychological effects is considered. New data are presented by Needleman and Winneke based on tooth lead levels, and also by Lansdown and his colleagues and David and colleagues, who have made important contributions in this field previously. The lively discussion included at the end of each chapter is a valuable critical addition to the material presented.

Despite the sensational title *Lead versus Health* which is a parody of the DHSS Lawther Report of 1980 *Lead and Health*, it is a remarkably sane book about a field where there is so much sensationalism. To be singled out for particular commendation are Rutter's introductory chapter, critically reviewing studies up to 1980 and stating the uncertainties of the position at that time and the even more masterly concluding chapter assessing the significance of more recent studies. For anyone who wants a balanced and critical summary this chapter is to be highly recommended. There are still very few certainties in the field, but a clear distinction is made between methodological difficulties in experimental studies and difficulties in interpretation of results.

It is comforting to inhabitants of the UK to realise that lead levels in children here are well below those found in the USA where many of the studies of lead effects were carried out. Lead levels in blood are falling in both countries and possible reasons are discussed.

PAMELA M. LE QUESNE

Atlas of Electroencephalography in the Child. By Paul Laget and Roger Salbreaux. 1982. Pp. 640. Paris: Masson. Price FF 880.00.

In the early development of electroencephalography it was soon discovered that brain function in the young mammal differed from that of the adult animal and in 1932 Hans Berger showed that the human brain was no exception. From that time interest in paediatric aspects of electroencephalography emerged especially in the USA (D. B. Linsley, J. R. Smith, F. A. Gibbs, J. R. Knott, C. E. Henry, amongst others). After the Second World War there was a rapidly increasing interest in Europe and three remarkable pioneers in France (Mesdames Dreyfus-Brisac, Samson-Dolfuss and Monod) published many papers on the development of the newborn in health and disease. Later in Switzerland, Guido Dumermuth produced a comprehensive book in German on paediatric EEG.

It was in about 1952 that Dr P. Laget emerged both as physiologist and as paediatric neurologist with his thesis on *Les Ondes Lentes dans l'EEG de L'enfant* (Paris). Soon afterwards he published several papers on paediatric EEG and in 1967 he coauthored with R. Salbreaux the *Atlas d'EEG Infantile* containing a great deal of information, illustrations and no less than 2352 references. This book, together with that of Dumermuth's (1964), were then considered the best available in the field of paediatric EEG.

With the establishment of clinical neurophysiology as a separate speciality and the rapid separation between adult and paediatric neurology, it has become necessary to learn how to use paediatric EEG in any medical centre dealing with newborn babies and young children. Over the last five years several good paediatric EEG books have appeared including the *Atlas of Neonatal EEG* by Werner, Stockard and Bickford (1977) and the *Atlas of EEG of Normal and Abnormal Infants from Birth to Eleven Months of Age* by Gibbs and Gibbs (1978). The new book by Laget and Salbreaux, *Atlas of Electroencephalography in the Child*, appeared in 1982 with a complete English text and includes not only modern techniques of recording, on methods of analysis and teletransmission, but also covers aspects of wakefulness and sleep. The EEG in the normal premature, the fullterm newborn, the first three months after birth, between the 3 months and 3 years, and from 3 to 15 years of age are well described. Brief but very useful sections cover Evoked Cortical Potentials (ECP) including somatosensory, visual and auditory modalities, with examples of normal and abnormal patterns. The appropriate ECP illustrations are clear but not perhaps the best in the book and certainly should be improved in the next edition.

The section on Pathological Features and their Maturation is rich in data and includes various types of clinical seizures and EEG manifestations both during wakefulness and during sleep. There is also a section on 'Activation Techniques', such as hyperventilation, photic stimulation and other types of stimuli including ocular compression and pharmacological effects upon EEG.

The main portion of the book is devoted to the 'EEG in neuropediatry', covering nearly 400 pages. It is divided into 'Acute encephalopathies' (with meningitis and encephalitis), and 'Chronic encephalopathy' (mostly orientated to EEG patterns in children with epilepsy but also including disorders with enzyme defects). This latter section is an expanding field, incomplete, and unfortunately the terminology in this area has become rather confused.

Several other sections are relatively short but useful with much information with clinical comments on 'Cerebral malformations', 'Complex dysmorphisms', 'Cranial-cerebral trauma', 'Headaches and migraine'. Several other EEG topics are 'Child neuro-psychiatry', 'Interictal psychic disorders', 'Personality disorders', 'Mental deficiency and retardation', and the so-called 'Minimal brain dysfunction'. These are briefly summarized and accompanied by extracts from individual EEG recordings. As usual in such patients, the evolution of each case is difficult to forecast and both clinical and EEG follow-up are essential. Various types of vascular lesions in infancy are nicely presented, although cerebral abscesses, brain tumours, hydrocephalus and anoxic states (at the end of the book) receive limited attention.

This book emphasizes that a pure clinical diagnosis and prognosis remain of limited value without appropriate EEG, CT scan and biochemical investigations, as everyone is now beginning to recognize. The remarkably extensive bibliography covers 62 pages with 2642 citations. There is also a useful index of 6 pages and a good index of authors (6 pages) completing this outstanding book. The English version will offer a much wider international readership and both the authors and the printers deserve warm congratulations.

G. PAMPIGLIONE

Computed Tomography in Intracranial Tumours. Edited by E. Kazner, S. Wende, T. Grumme, W. Lanksch and O. Stochdorph. 1982. Pp. 548. Berlin, Heidelberg, New York: Springer-Verlag. Price DM 448.00.

This book presents experience gained in the diagnosis of intracranial tumours using computed tomography in a cooperative study between the University Hospitals of Berlin, Mainz and Munich and is based on comparison of the computed tomographic surgical and neuropathological studies of over 3,750 patients with brain tumours and 600 with orbital lesions. The authors include distinguished neuropathologists, neurosurgeons and neuroradiologists of international reputation.

The format of the book is good for both teaching and easy reference. It commences with a brief but clear and well referenced explanation of the classification of intracranial tumours followed by short chapters on the authors' technique of CT examination and explanation of the criteria used in evaluation. Most of the book is devoted to analysis of the CT features of the various histological types of tumour and of the nonneoplastic lesions which may simulate them.

Each chapter commences with a summary of the clinical and more typical radiological manifestations which should prove particularly valuable for examination candidates. The illustrations are superb; it could be argued that there is over illustration with its inevitable contribution to the cost of publication. However, the authors use the captions well to emphasize particular points in the text and such features as the nonspecific nature of many CT appearances and also mention both misinterpretations and other diagnostic possibilities, which adds greatly to the reader's interest and enjoyment.

There is a good balance between the necessary emphasis on relatively common tumours and presentation of the more helpful diagnostic features of even the rarest lesions. The English is excellent, the references are up to date and cover the relevant European and American literature and the index is comprehensive.

The book is strongly recommended for departmental reference and to those training in the neurosciences.

B. E. KENDALL

Axoplasmic Transport in Physiology and Pathology. Edited by D. G. Weiss and A. Gorio. 1982. Pp. 192. Berlin: Springer-Verlag. Price DM 78.00.

This book was conceived at the occasion of the 'Workshop on Axoplasmic Transport' which was held at the Schloss Elmau in Bavaria in 1981. It is a companion to another book edited by D. G. Weiss entitled *Axoplasmic Transport* which is published concomitantly. This particular volume deals with the physiology and pathology of axoplasmic transport and is intended to be of interest to neurologists, neurosurgeons, neurotoxicologists, neuropathologists, ophthalmologists, dentists and others dealing with the medical aspects of neurons in the nervous system, the more basic aspects of the subject being covered in *Axoplasmic Transport.* The first section covers general properties of axoplasmic transport and the physiological role of this mechanism. Later sections include the role of axoplasmic transport in growth and regeneration and changes seen in experimental neuropathies and diseases and experimental damage to the nervous system. The final section describes axoplasmic transport as a tool in neurophysiology and neuroanatomy. For a reader not actively involved in research this book provides a fascinating overview of the mechanisms and scope of axoplasmic transport, in particular the bidirectional nature of this transport, the categories of materials transported and the energy utilization involved. The extent to which these mechanisms are important for normal physiological growth and for repair are described in several papers based on experimental models including the goldfish optic nerve and parts of the brain on the optic pathway in other species. Also described are studies of the transneuronal transports of adenonucleotides which indicate the possibility of adenosine as a modulatory factor for neuronal signals and involved in the central role of neuropeptides. Defects in axonal transport in relation to diseases of the optic nerve and retina and in degenerative diseases of the nervous system are discussed, as are the implications of axoplasmic transport for the spread of virus infections in the nervous system.

It has to be admitted that it is likely that the contents of this book are still rather distant from the experience and interest of clinicians. However, its concise and clear presentation has much to commend it to clinicians who wish to have their eyes opened to this new and exciting field. Its price would seem to be appropriate.

R. H. T. EDWARDS

Progress in Sensory Physiology. Volume 3. **Control of Nociceptive Transmission in the Spinal Cord.** By W. D. Willis. 1982. Pp. 159. Berlin: Springer-Verlag. Price DM 69.00.

A series of reviews of topics is being published as *Progress in Sensory Physiology.* The first two volumes contained a number of distinguished reviews. This third volume is on a single subject by Willis who is a major contributor to the field and is also the author with Coggeshall of a comprehensive text in 1978 of *Sensory Mechanisms of the Spinal Cord* (New York· Plenum). The present review necessarily repeats some of that text but brings it up to date and concentrates on the particular issue. As is fashionable, the word control is mainly discussed in terms of descending controls from the brainstem which influence local segmental mechanisms. After an introduction the five chapters discuss behavioural evidence for descending control, the pharmacology of analgesia due to descending control systems, descending control of the flexion reflex, descending control of nociceptive neurons and finally correlations between descending controls and analgesia. It will be seen that two quite different bodies of evidence are presented. One deals with manipulations of the central nervous system which produce analgesia as measured by some behavioural test. The other describes the inhibitory effects of stimulation on the response of single cells in the spinal cord. The author is very honest in his caution on the correlation between these two types of evidence. The book is a cautious comprehensive review of the state of the art without novel proposals for ways out of the implied paradoxes. The state of the art is necessarily dependent on the state of the techniques which were used. New thinking and new techniques will be required to answer a series of questions. Are the animal tests measuring analgesia? What is the relation between the firing of cells and their control systems and the behavioural state of the man or animal? Is it sufficient to study sudden responses to sudden stimuli or are there additional mechanisms which change the response of the nervous system over minutes, hours and days?

PATRICK D. WALL

ANNOUNCEMENTS

Joint World Meeting on Neuro-ophthalmology and Neurogenetics

Antwerp (Belgium) May 14–18, 1984

This will combine the Fifth Meeting of the International Society of Neuro-ophthalmology and the Seventh Congress of the Study Group of Neuro-ophthalmology and Neurogenetics of the World Federation of Neurology.

The topics to be discussed will include ocular motor symptoms related to stereotaxic treatment, supranuclear ocular motor abnormalities in metabolic disease, mechanism of action of ocular muscle transplants, secondary muscular neurotization, pseudotumour cerebri, digital subtraction angiography, nuclear magnetic resonance, oligosaccharidoses, cerebral neurotransmitters, disturbance of accommodation and square wave jerk nystagmus, leucodystrophies, Fabry's disease, Wolfram syndrome, and neuro-ophthalmological features of developmental anomalies.

For further information please contact Professor A. Neetens, Academic Hospital, University of Antwerp, Wilrijkstraat 10, 2520 Edegem, Belgium. (Telephone (03) 829.11.11. extension 1337-79).

PNAA Symposium on Diabetic Neuropathy

An international symposium on diabetic neuropathy sponsored by the Peripheral Neuropathy Association of America (PNAA) will be held at Keystone, Colorado, on June 19–22, 1984. The objective of the meeting is to bring together leading investigators from different disciplines to describe the clinical, cellular and molecular derangements and to identify mechanisms related to the development of neuropathy and its symptoms. A small number of promising young investigators interested in a future career in metabolic or peripheral nerve research will be invited to participate. Symposia on natural history and epidemiology, grading and monitoring of the neuropathy, clinical trials, pathological alterations, nerve microenvironment, microvascular derangement, axonal flow, lipid metabolism, inositol and other cyclitols, and open sessions are planned. Attendance will be limited to 150 persons invited as a resource scientist, accepted by approved abstract, or selected as a promising young scientist. Partial financial support is available for all participants. The deadline for abstracts and nominating letters is January 15, 1984. Further information regarding submission of abstracts and nomination of promising young investigators may be obtained from Dr P. J. Dyck, Mayo Clinic, Rochester, MN, 55905, USA.

International Symposium in honour of Professor Henri Gastaut
'The epileptic syndromes: clinical and evolutive aspects'

An International Symposium in honour of Professor Henri Gastaut, concerning 'The epileptic syndromes: clinical and evolutive aspects', will be held in Bologna (Italy), on September 26–29, 1984, at Palazzo dei Congressi. The presidents of the Organizing Committee are E. Lugaresi and C. A. Tassinari. Further information may be obtained from the Secretary, Dr P. Pazzaglia, Istituto di Neurologia, Via Ugo Foscolo 7, 40123 Bologna, Italy.

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INDEX FOR VOL. 106, 1983

AUTHORS

PAGE

ABBRUZZESE G. *See* RATTO S. 897

ABBRUZZESE M. *See* RATTO S 897

ALLPRESS S. *See* POLLOCK M 911

ANDREW J, FOWLER C J, HARRISON M J G. Stereotaxic thalamotomy in 55 cases of dystonia 981

BABB T L. *See* WILSON C L 473

BANNISTER R. *See* PURITZ R 503

BERCIANO J. *See* REBOLLO M 965

BERNARDI S. *See* WISE R J S 197

BLUME W T. *See* YOUNG G B 537

BRANDT TH. *See* WIST E R 153

BRIMIJOIN W S. *See* DYCK P J 373

BRODAL P. *See* SLOPER J J 707

BROWN S M. *See* KENNEDY P G E 101

BRUNNER R J. *See* WALLESCH C W 141

CABELLO A. *See* RICOY J R 817

CALTAGIRONE C. *See* GAINOTTI G 613

CARTER N D. *See* SWASH M 717

CHAMBERS B. *See* FISHER A 949

CHANNING M A. *See* DUARA R 761

PAGE

CHEN L S. *See* SCHADY W 745

CLEMENTS G B. *See* KENNEDY P G E 101

CORKIN S. *See* EICHENBAUM H 459

COURJON J. *See* MAUGUIÈRE F 271

CRANDALL P H. *See* WILSON C L 473

CROSS M J. *See* MCCLOSKEY D I 21

CUTLER N R. *See* DUARA R 761

DAUBE J R. *See* DYCK P J 373

DELOCHE G. *See* SERON X 735

DESMEDT J E. *See* MAUGUIÈRE F 271

DUARA R, MARGOLIN R A, ROBERTSON-TCHABO E A, LONDON E D, SCHWARTZ M, RENFREW J W, KOZIARZ B J, SUNDARUM M, GRADY C, MOORE A M, INGVAR D H, SOKOLOFF L, WEINGARTNER H, KESSLER R M, MANNING R G, CHANNING M A, CUTLER N R, RAPOPORT S I. Cerebral glucose utilization, as measured with positron emission tomography in 21 resting healthy men between the ages of 21 and 83 years 761

DYCK P J, MELLINGER J F, REAGAN T J, HOROWITZ J, MCDONALD J W, LITCHY W J, DAUBE J R, FEALEY R D, GO V L, KAO P C, BRIMIJOIN W S, LAMBERT E H. Not 'indifference to pain' but varieties of hereditary sensory and autonomic neuropathy 373

EAMES R A. *See* SMITH I S 169

EBERS G C. *See* MOULIN D 809

EERBEEK J M. *See* STENVERS J-W 601

EICHENBAUM H, MORTON T H, POTTER H, CORKIN S. Selective olfactory deficits in Case H.M. 459

FAGIUS J, WALLIN B G. Microneurographic evidence of excessive sympathetic outflow in the Guillain-Barré syndrome 589

FAVALE E. *See* RATTO S 897

FEALEY R D, *See* DYCK P J 373

FISHER A, GRESTY M, CHAMBERS B, RUDGE P. Primary position upbeating nystagmus: a variety of central positional nystagmus 949

FORSLING M. *See* PURITZ R 503

FOWLER C J. *See* ANDREW J 981

FRACKOWIAK R S J. *See* WISE R J S 197

FRITH R W. *See* POLLOCK M 911

GAINOTTI G, SILVERI M C, VILLA G, CALTAGIRONE C. Drawing objects from memory in aphasia 613

PAGE
Gardner H. *See* Judd T 435
Garijo F. *See* Rebollo M 965
Geschwind N. *See* Judd T 435
Gleason C A. *See* Libet B 623
Go V L. *See* Dyck P J 373
Grady C. *See* Duara R 761
Gresty M. *See* Fisher A 949
Hahn J. *See* Lueders H 341
Halgren E. *See* Wilson C L 473
Harrison M J G. *See* Andrew J 981
Heath R. *See* Swash M 717
Heilman K M. *See* Watson R T 391
Henderson V W. Speech fluency in crossed aphasia 837
Hill G O. *See* Vrtunski P B 929
Hirai T, Miyazaki M, Nakajima H, Shibazaki T, Ohye C. The correlation between tremor characteristics and the predicted volume of effective lesions in stereotaxic Vim. thalamotomy 1001
Hogenhuis L A H. *See* Reulen J P H 121
Honner R. *See* McCloskey D I 21
Horowitz S J. *See* Dyck P J 373
Igisu H, Shimomura K, Kishimoto Y, Suzuki K. Lipids of developing brain of twitcher mouse: an authentic murine model of human Krabbe disease 405
Ikeda H. *See* Tremain K E 879
Ingvar D H. *See* Duara R 761
Jones T. *See* Wise R J S 197
Judd T, Gardner H, Geschwind N. Alexia without agraphia in a composer 435
Kahn S N. *See* Smith I S 169
Kao P C. *See* Dyck P J 373
Karson C N. Spontaneous eye-blink rates and dopaminergic systems 643
Kennedy P G E, Clements G B, Brown S M. Differential susceptibility of human neural cell types in culture to infection with herpes simplex virus 101
Kessler R G. *See* Duara R 761
King R H M. *See* Smith I S 169
Kishimoto Y. *See* Igisu H 405
Klem G. *See* Lueders H 341

PAGE

Kornhuber H H. *See* Wallesch C W 141

Koziarz B J. *See* Duara R 761

Krafczyk S. *See* Wist E R 153

Kunz T. *See* Wallesch C W 141

Lacey B W. *See* Smith I S 169

Lambert E H. *See* Dyck P J 373

Leak M. *See* Swash M 717

Lees A J, Smith E. Cognitive deficits in the early stages of Parkinson's disease 257

Legg N J. *See* Wise R J S 197

Lesser R. *See* Lueders H 341

Lhermitte F. 'Utilization behaviour' and its relation to lesions of the frontal lobes 237

Libet B, Gleason C A, Wright E W, Pearl D K. Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential): the unconscious initiation of a freely voluntary act 623

Lightman S L. *See* Puritz R 503

Litchy W J. *See* Dyck P J 373

Little J. *See* Lueders H 341

London E D. *See* Duara R 761

Love S. An experimental study of peripheral nerve regeneration after x-irradiation 39

Lueders H, Lesser R, Hahn J, Little J, Klem G. Subcortical somatosensory evoked potentials to median nerve stimulation 341

McCarthy R. *See* Warrington E K 859

McCloskey D I, Cross M J, Honner R, Potter E K. Sensory effects of pulling or vibrating exposed tendons in man 21

McDonald J W. *See* Dyck P J 373

Mack J L. *See* Vrtunski P B 929

Mai N. *See* Zihl J 313

Manning M A. *See* Duara R 761

Margolin R A. *See* Duara R 761

Masuzawa T, Sato F. The enzyme histochemistry of the choroid plexus 55

Matelli M. *See* Rizzolatti G 655

Mauguière F, Desmedt J E, Courjon J. Astereognosis and dissociated loss of frontal or parietal components of somatosensory evoked potentials in hemispheric lesions: detailed correlations with clinical signs and computerized tomographic scanning 271

PAGE

MEIJER A E F H. *See* STENVERS J-W 601

MELLINGER J F. *See* DYCK P J 373

MIYAZAKI M. *See* HIRAI T 1001

MOBERG E. The role of cutaneous afferents in position sense, kinaesthesia, and motor function of the hand 1

MOORE A M. *See* DUARA R 761

MORTON T H. *See* EICHENBAUM H 459

MOULIN D, PATY D W, EBERS G C. The predictive value of CSF electrophoresis in 'possible' multiple sclerosis 809

NAKAJIMA H. *See* HIRAI T 1001

NUKADA H. *See* POLLOCK M 911

OCHOA J L. *See* SCHADY W 745

OHYE C. *See* HIRAI T 1001

PAGE N G R. *See* ROSS RUSSELL R W 419

PASSINGHAM R E, PERRY V H, WILKINSON F. The long-term effects of removal of sensorimotor cortex in infant and adult Rhesus monkeys 675

PATTERSON M B. *See* VRTUNSKI P B 929

PATY D W. *See* MOULIN D 809

PAVESI G. *See* RIZZOLATTI G 655

PEARL D K. *See* GLEASON C A 623

PERRY V H. *See* PASSINGHAM R E 675

POLLOCK M, NUKADA H, FRITH R W, SIMCOCK J P, ALLPRESS S. Peripheral neuropathy in Tangier disease 911

POTTER E K. *See* MCCLOSKEY D I 21

POTTER H. *See* EICHENBAUM H 459

POWELL T P S. *See* SLOPER J J 707

PURITZ R, LIGHTMAN S L, WILCOX C S, FORSLING M, BANNISTER R. Blood pressure and vasopressin in progressive autonomic failure: response to postural stimulation, L-DOPA and naloxone 503

QUINTANA F. *See* REBOLLO M 965

RAPOPORT S I. *See* DUARA R 761

RATTO S, ABBRUZZESE M, ABBRUZZESE G, FAVALE E. Surface recording of the spinal ventral root discharge in man: an experimental study 897

REAGAN T J. *See* DYCK P J 373

REBOLLO M, VAL J F, GARIJO F, QUINTANA F, BERCIANO J. Livedo reticularis and cerebrovascular lesions (Sneddon's syndrome): clinical radiological and pathological features in 8 cases 965

PAGE

RENFREW J W. *See* DUARA R 761

REULEN J P H, SANDERS E A C M, HOGENHUIS L A H. Eye movement disorders in multiple sclerosis and optic neuritis 121

RICOY J R, CABELLO A, RODRIGUEZ J, TELLÉZ I. Neuropathological studies of the toxic syndrome related to adulterated rapeseed oil in Spain 817

RIZZOLATTI G, MATELLI M, PAVESI G. Deficits in attention and movement following the removal of postarcuate (area 6) and prearcuate (area 8) cortex in Macaque monkeys 655

ROBERTSON-TCHABO E A. *See* DUARA R 761

RODRIGUEZ J. *See* RICOY J R 817

ROGERS K Ll. *See* SWASH M 717

ROSS RUSSELL R W, PAGE N G R. Critical perfusion of brain and retina 419

RUDGE P. *See* FISHER A 949

SAID G, SLAMA G, SELVA J. Progressive centripetal degeneration of axons in small fibre type diabetic polyneuropathy 791

SAINT-CYR J A. *See* WHITE O B 555, 571

SANDERS E A C M. *See* REULEN J P H 121

SATO F. *See* MASUZAWA T 55

SCHADY W, OCHOA J L, TOREBJÖRK H E, CHEN L S. Peripheral projections of fascicles in the human median nerve 745

SCHWARTZ M. *See* DUARA R 761

SCHWARTZ M S. *See* SWASH M 717

SELVA J. *See* SAID G 791

SERON X, DELOCHE G. From 4 to four: a supplement to 'from three to 3' 735

SHARPE J A. *See* WHITE O B 555, 571

SHIBAZAKI T. *See* HIRAI T 1001

SHIMOMURA K. *See* IGISU H 405

SILVERI M C. *See* GAINOTTI G 613

SIMCOCK J P. *See* POLLOCK M 911

SLAMA G. *See* SAID G 791

SLOPER J J, BRODAL P, POWELL T P S. An anatomical study of the effects of unilateral removal of sensorimotor cortex in infant monkeys on the subcortical projections of the contralateral sensorimotor cortex 707

SMITH E. *See* Lees A J 257

SMITH I S, KAHN S N, LACEY B W, KING R H M, EAMES R A, WHYBREW D J, THOMAS P K. Chronic demyelinating neuropathy associated with benign IgM paraproteinaemia 169

PAGE

Sokoloff L. *See* Duara R 761

Stenvers J-W, Eerbeek J M, Vianney de Jong J M B, Meijer A E F H. Motor activity and muscle properties in the hemidecerebellate cat 601

Sundarum M. *See* Duara R 761

Suzuki K. *See* Igisu H 405

Swash M, Schwartz M S, Carter N D, Heath R, Leak M, Rogers K Ll. Benign X-linked myopathy with acanthocytes (McLeod syndrome): its relationship to X-linked muscular dystrophy 717

Telléz I. *See* Ricoy J R 817

Thomas P K. *See* smith I S 169

Tomlinson R D. *See* White O B 571

Torebjörk H E. *See* Schady W 745

Tremain K E, Ikeda H. Physiological deficits in the visual system of mice infected with Semliki Forest virus and their correlation with those seen in patients with demyelinating disease 879

Val J F. *See* Rebollo M 965

Vianney de Jong J M B. *See* Stenvers J-W 601

Villa G. *See* Gainotti G 613

von Cramon D. *See* Zihl J 313

Vrtunski P B, Patterson M B, Mack J L, Hill G O. Microbehavioural analysis of the choice reaction time response in senile dementia 929

Wade J P H. Transport of oxygen to the brain in patients with elevated haematocrit values before and after venesection 513

Wallesch C W, Kornhuber H H, Kunz T, Brunner R J. Neuropsychological deficits associated with small unilateral thalamic lesions 141

Wallin B G. *See* Fagius J 589

Warrington E K, McCarthy R. Category specific access dysphasia 859

Watson R T, Heilman K M. Callosal apraxia 391

Weingartner H. *See* Duara R 761

White O B, Saint-Cyr J A, Sharpe J A. Ocular motor deficits in Parkinson's disease. I. The horizontal vestibulo-ocular reflex and its regulation 555

White O B, Saint-Cyr J A, Tomlinson R D, Sharpe J A. Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems 571

Whybrew D J. *See* Smith I S 169

Wilcox C S. *See* Puritz R 503

Wilkinson F. *See* Passingham R E 675

PAGE

WILSON C L, BABB T L, HALGREN E, CRANDALL P H. Visual receptive fields and response properties of neurons in human temporal lobe and visual pathways 473

WISE R J S, BERNARDI S, FRACKOWIAK R S J, LEGG N J, JONES T. Serial observations on the pathophysiology of acute stroke: the transition from ischaemia to infarction as reflected in regional oxygen extraction 197

WIST E R, BRANDT TH, KRAFCZYK S. Oscillopsia and retinal slip: evidence supporting a clinical test 153

WRIGHT E W. *See* GLEASON C A 623

YOUNG G B, BLUME W T. Painful epileptic seizures 537

ZIHL J, VON CRAMON D, MAI N. Selective disturbance of movement vision after bilateral brain damage 313

SUBJECTS

Acanthocytes, in benign X-linked myopathy (McLeod syndrome): its relationship to X-linked muscular dystrophy (Swash *et al.*) 717

Alexia without agraphia in a composer (Judd *et al.*) 435

Anatomical study of the effects of unilateral removal of sensorimotor cortex in infant monkeys on the subcortical projections of the contralateral sensorimotor cortex (Sloper *et al.*) 707

Aphasia, crossed, speech fluency in (Henderson) 837

Aphasia, drawing objects from memory in (Gainotti *et al.*) 613

Apraxia, callosal (Watson and Heilman) 391

Astereognosis and dissociated loss of frontal or parietal components of somatosensory evoked potentials in hemispheric lesions: detailed correlations with clinical signs and computerized tomographic scanning (Mauguière *et al.*) 271

Autonomic failure, progressive, blood pressure and vasopressin in: response to postural stimulation, L-DOPA and naloxone (Puritz *et al.*) 503

Benign X-linked myopathy with acanthocytes (McLeod syndrome): its relationship to X-linked muscular dystrophy (Swash *et al.*) 717

Blood pressure and vasopressin in progressive autonomic failure: response to postural stimulation, L-DOPA and naloxone (Puritz *et al.*) 503

Callosal apraxia (Watson and Heilman) 391

Category specific access dysphasia (Warrington and McCarthy) 859

PAGE

Cerebral glucose utilization as measured with positron emission tomography in 21 resting healthy men between the ages of 21 and 83 years (Duara *et al.*) 761

Cerebrovascular lesions, livedo reticularis and (Sneddon's syndrome): clinical, radiological and pathological features in 8 cases (Rebollo *et al.*) 965

Choroid plexus, enzyme histochemistry (Masuzawa and Sato) 55

Chronic demyelinating neuropathy associated with benign IgM paraproteinaemia (Smith *et al.*) 169

Cognitive deficits in the early stages of Parkinson's disease (Lees and Smith) 257

Conscious intention to act, time of, in relation to onset of cerebral activity (readiness-potential): the unconscious initiation of a freely voluntary act (Libet *et al.*) 623

Correlation between tremor characteristics and the predicted volume of effective lesions in stereotaxic Vim. thalamotomy (Hirai *et al.*) 1001

Cortex, postarcuate, deficits in attention and movement following removal of, and of prearcuate cortex in Macaque monkeys (Rizzolatti *et al.*) 655

Cortex, prearcuate, deficits in attention and movement following the removal of, and of postarcuate cortex, in Macaque monkeys (Rizzolatti *et al.*) 655

Cortex, sensorimotor, anatomical study of effects of unilateral removal of, on subcortical projections of the contralateral sensorimotor cortex in infant monkeys (Sloper *et al.*) 707

Cortex, sensorimotor, long-term effects of removal of, in infant and adult Rhesus monkeys (Passingham *et al.*) 675

Critical perfusion of brain and retina (Ross Russell and Page) 419

Crossed aphasia, speech fluency in (Henderson) 837

CSF electrophoresis, predictive value in 'possible' multiple sclerosis (Moulin *et al.*) 809

Deficts in attention and movement following the removal of postarcuate and prearcuate cortex in Macaque monkeys (Rizzolatti *et al.*) 655

Dementia, senile, microbehavioral analysis of the choice reaction time response in (Vrtunski *et al.*) 929

Diabetic polyneuropathy, progressive centripetal degeneration of axons in small fibre type (Said *et al.*) 791

Differential susceptibility of human neural cell types in culture to infection with herpes simplex virus (Kennedy *et al.*) 101

Dopaminergic systems, spontaneous eye-blink rates and (Karson) 643

Drawing objects from memory in aphasia (Gainotti *et al.*) 613

Dysphasia, category specific access (Warrington and McCarthy) 859

Dystonia, stereotaxic thalamotomy in 55 cases of (Fowler *et al.*) 981

	PAGE
Enzyme histochemistry of the choroid plexus (Masuzawa and Sato)	55
Epileptic seizures, painful (Young and Blume)	537
Experimental study of peripheral nerve regeneration after x-irradiation (Love)	39
Eye movement disorders in multiple sclerosis and optic neuritis (Reulen *et al.*)	121
Eye-blink rates, spontaneous, and dopaminergic systems (Karson)	643
From 4 to four: a supplement to 'from three to 3' (Seron and Deloche)	735
Frontal lobes, 'utilization behaviour' and its relation to lesions of (Lhermitte)	237
Glucose utilization, cerebral, as measured with position emission tomography in 21 resting healthy men between the ages of 21 and 83 years (Duara *et al.*)	761
Guillain-Barré syndrome, microneurographic evidence of excessive sympathetic outflow in (Fagius and Wallin)	589
Haematocrit, elevated, transport of oxygen to the brain in patients with, values before and after venesection (Wade)	513
Hemidecerebellate cat, motor activity and muscle properties in (Stenvers *et al.*)	601
Herpes simplex virus, differential susceptibility of human neural cell types in culture to infection with (Kennedy *et al.*)	101
Kinaesthesia: role of cutaneous afferents in, and in position sense, and motor function of the hand (Moberg)	1
Lipids of developing brain of twitcher mouse: an authentic murine model of human Krabbe disease (Igisu *et al.*)	405
Livedo reticularis and cerebrovascular lesions (Sneddon's syndrome): clinical, radiological and pathological features in 8 cases (Rebollo *et al.*)	965
Long-term effects of removal of sensorimotor cortex in infant and adult Rhesus monkeys (Passingham *et al.*)	675
McLeod syndrome, benign X-linked myopathy with acanthocytes: its relationship to X-linked muscular dystrophy (Swash *et al.*)	717
Microbehavioral analysis of the choice reaction time response in senile dementia (Vrtunski *et al.*)	929
Microneurographic evidence of excessive sympathetic outflow in the Guillain-Barré syndrome (Fagius and Wallin)	589
Motor activity and muscle properties in the hemidecerebellate cat (Stenvers *et al.*)	601
Movement vision, selective disturbance of, after bilateral brain damage (Zihl *et al.*)	313
Multiple sclerosis, eye movement disorders in, and in optic neuritis (Reulen *et al.*)	121
Multiple sclerosis, predictive value of CSF electrophoresis (Moulin *et al.*)	809
Muscle properties, and motor activity, in the hemidecerebellate cat (Stenvers *et al.*)	601
Muscular dystrophy, X-linked, benign X-linked myopathy with acanthocytes (McLeod syndrome), its relationship to (Swash *et al.*)	717

PAGE

Myopathy, benign X-linked, with acanthocytes (McLeod syndrome): its relationship to X-linked muscular dystrophy (Swash *et al.*) 717

Nerve, human median, peripheral projections of fascicles in (Schady *et al.*) 745

Nerve, peripheral: experimental study of regeneration after x-irradiation (Love) 39

Neuropathological studies of the toxic syndrome related to adulterated rapeseed oil in Spain (Ricoy *et al.*) 817

Neuropathy, chronic demyelinating, associated with benign IgM paraproteinaemia (Smith *et al.*) 169

Neuropathy, diabetic, progressive centripetal degeneration of axons in small fibre type (Said *et al.*) 791

Neuropathy, not 'indifference to pain' but varieties of hereditary sensory and autonomic (Dyck *et al.*) 373

Neuropathy, peripheral, in Tangier disease (Pollock *et al.*) 911

Neuropsychological deficits associated with small unilateral thalamic lesions (Wallesch *et al.*) 141

Not 'indifference to pain' but varieties of hereditary sensory and autonomic neuropathy (Dyck *et al.*) 373

Nystagmus, primary position upbeating, a variety of central positional nystagmus (Fisher *et al.*) 949

Ocular motor deficits in Parkinson's disease: I. The horizontal vestibulo-ocular reflex and its regulation (White *et al.*) 555

Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems (White *et al.*) 571

Oil, adulterated rapeseed, in Spain, neuropathological studies of the toxic syndrome related to (Ricoy *et al.*) 817

Olfactory deficits, selective, in Case H.M. (Eichenbaum *et al.*) 459

Optic neuritis, eye movement disorders in, and in multiple sclerosis (Reulen *et al.*) 121

Oscillopsia and retinal slip: evidence supporting a clinical test (Wist *et al.*) 153

Painful epileptic seizures (Young and Blume) 537

Paraproteinaemia, benign IgM, chronic demyelinating neuropathy associated with (Smith *et al.*) 169

Parkinson's disease, cognitive deficits in the early stages of (Lees and Smith) 257

Parkinson's disease, ocular motor deficits in. I. The horizontal vestibulo-ocular reflex and its regulation (White *et al.*) 555

Parkinson's disease, ocular motor deficits in. II. Control of the saccadic and smooth pursuit systems (White *et al.*) 571

PAGE

Perfusion, critical, of brain and retina (Ross Russell and Page) 419

Peripheral neuropathy in Tangier disease (Pollock *et al.*) 911

Peripheral projections of fascicles in the human median nerve (Schady *et al.*) 745

Physiological deficits in the visual system of mice infected with Semliki Forest virus and their correlation with those seen in patients with demyelinating disease (Tremain and Ikeda) 879

Position sense; role of cutaneous afferents and kinaesthesia in, and in motor function of the hand (Moberg) 1

Positron emission tomography, cerebral glucose utilization, in 21 resting healthy men between the ages of 21 and 83 years (Duara *et al.*) 761

Predictive value of CSF electrophoresis in 'possible' multiple sclerosis (Moulin *et al.*) 809

Primary position upbeating nystagmus: a variety of central positional nystagmus (Fisher *et al.*) 949

Progressive centripetal degeneration of axons in small fibre type diabetic polyneuropathy (Said *et al.*) 791

Rapeseed oil, adulterated, in Spain, neuropathological studies of the toxic syndrome related to (Ricoy *et al.*) 817

Readiness-potential, time of conscious intention to act in relation to onset of cerebral activity, the unconscious initiation of a freely voluntary act (Libet *et al.*) 623

Retina, critical perfusion of brain and (Ross Russell and Page) 419

Retinal slip, oscillopsia: evidence supporting a clinical test (Wist *et al.*) 153

Role of cutaneous afferents in position sense, kinaesthesia, and motor function of the hand (Moberg) 1

Selective disturbance of movement vision after bilateral brain damage (Zihl *et al.*) 313

Selective olfactory deficits in Case H.M. (Eichenbaum *et al.*) 459

Semliki Forest virus, physiological deficits in the visual system of mice infected with, and their correlation with those seen in patients with demyelinating disease (Tremain and Ikeda) 879

Senile dementia, microbehavioural analysis of the choice reaction time response in (Vrtunski *et al.*) 929

Sensory effects of pulling or vibrating exposed tendons in man (McCloskey *et al.*) 21

Serial observations on the pathophysiology of acute stroke: the transition from ischaemia to infarction as reflected in regional oxygen extraction (Wise *et al.*) 197

Sneddon's syndrome, livedo reticularis and cerebrovascular lesions, clinical, radiological and pathological features in 8 cases (Rebollo *et al.*) 965

PAGE

Somatosensory evoked potentials, astereognosis and dissociated loss of frontal or parietal components, in hemispheric lesions: detailed correlations with clinical signs and computerized tomographic scanning (Mauguière *et al.*) 271

Somatosensory evoked potentials, subcortical, to median nerve stimulation (Lueders *et al.*) 341

Speech fluency in crossed aphasia (Henderson) 837

Spinal ventral root discharge, surface recording of, in man: an experimental study (Favale *et al.*) 897

Spontaneous eye-blink rates and dopaminergic systems (Karson) 643

Stereotaxic thalamotomy in 55 cases of dystonia (Andrew *et al.*) 981

Stroke, serial observations on the pathophysiology of acute; the transition from ischaemia to infarction as reflected in regional oxygen extraction (Wise *et al.*) 197

Subcortical somatosensory evoked potentials to median nerve stimulation (Lueders *et al.*) 341

Surface recording of the spinal ventral root discharge in man: an experimental study (Favale *et al.*) 897

Tangier disease, peripheral neuropathy in (Pollock *et al.*) 911

Tendons, exposed, sensory effects of pulling or vibrating in man (McCloskey *et al.*) 21

Thalamotomy, stereotaxic, in 55 cases of dystonia (Andrew *et al.*) 981

Thalamotomy, Vim. the correlation between tremor characteristics and the predicted volume of effective stereotaxic lesions (Hirai *et al.*) 1001

Thalamus, neuropsychological deficits associated with small unilateral lesions in (Wallesch *et al.*) 141

Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential): the unconscious initiation of a freely voluntary act (Libet *et al.*) 623

Transport of oxygen to the brain in patients with elevated haematocrit values before and after venesection (Wade) 513

Tremor, correlation between characteristics of and the predicted volume of effective lesions in stereotaxic Vim. thalamotomy (Hirai *et al.*) 1001

Twitcher mouse, an authentic murine model of human Krabbe disease, lipids of developing brain of (Igisu *et al.*) 405

'Utilization behaviour' and its relation to lesions of the frontal lobes (Lhermitte) 237

Ventral root discharge, spinal, surface recording of in man: an experimental study (Ratto *et al.*) 897

Virus, herpes simplex, differential susceptibility of human neural cell types in culture to infection with (Kennedy *et al.*) 101

PAGE

Virus, Semliki Forest, physiological deficits in the visual system of mice infected with, and their correlation with those seen in patients with demyelinating disease (Tremain and Ikeda) 879

Visual receptive fields and response properties of neurons in human temporal lobe and visual pathways (Wilson *et al.*) 473

Visual system, physiological deficits of, in mice infected with Semliki Forest virus and their correlation with those seen in patients with demyelinating disease (Tremain and Ikeda) 879

X-irradiation, experimental study of peripheral nerve regeneration after (Love) 39

Travel Grants For Young Neuroscientists

The Guarantors of Brain are prepared to consider applications for contributions towards travel costs from neuroscientists under the age of 40 working in the United Kingdom.

1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:
    - (a) An abbreviated curriculum vitae and a list of any relevant publications;
    - (b) Statement of age and post currently held;
    - (c) A concise account of the purpose of the proposed visit;
    - (d) A recommendation from the Head of Department (where appropriate);
    - (e) A letter of acceptance from the Department to be visited;
    - (f) A statement of costs likely to be incurred, and of other applications for funds that have been made. Advantage should always be taken of reduced air fares when available.

2. Applications will also be considered for contributions to the cost of attending specialized symposia of particular importance to the applicant's research. Documents as in (a), (b), (c), (d) and (f) above should be submitted at least three months before the date of the meeting, accompanied by a statement of what other applications for financial aid have been made and of any contributions by the symposium organization.

3. Only exceptionally will applications for assistance to attend larger international congresses be entertained.

Successful applicants will be expected to submit a brief report on the conclusion of their visit.

Four copies of all documents should be submitted to

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